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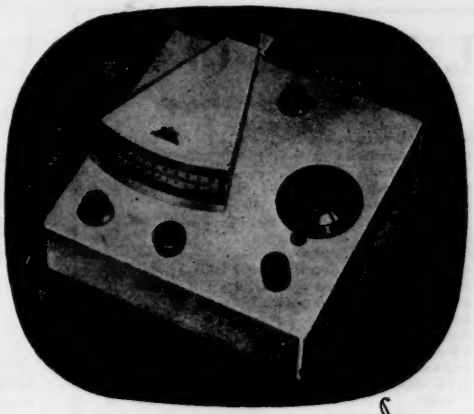

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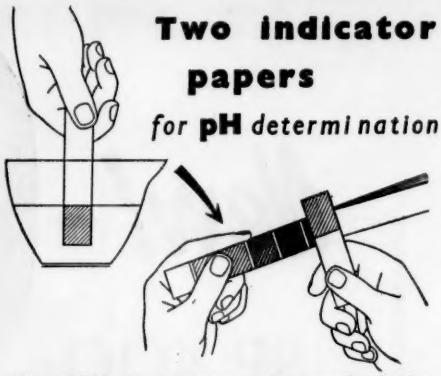

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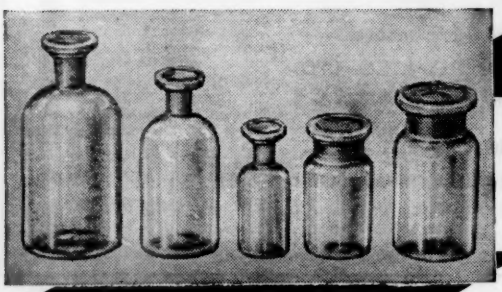

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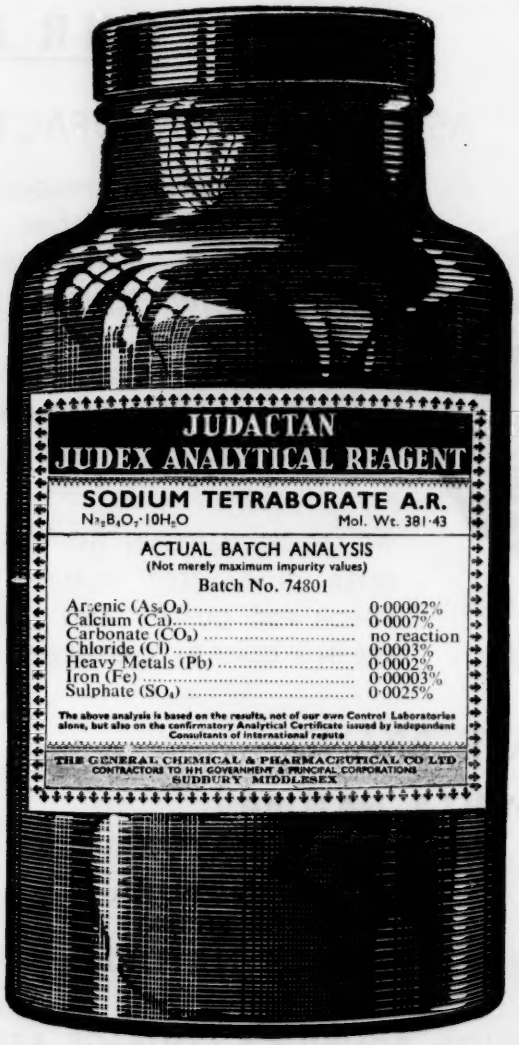
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Calcium (Ca) 0·0007%
Carbonate (CO_3) no reaction
Chloride (Cl) 0·0003%
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Iron (Fe) 0·00003%
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*The Chemistry of Humulene. Part IV.**

By R. W. Fawcett and J. O. Harris.

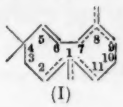
[Reprint Order No. 5133.]

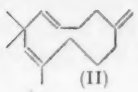
3 : 7 : 7 : 10- or 2 : 6 : 6 : 9-Tetramethylundecane-1 : 11-dioic acid has been prepared and shown to be identical with the C_{15} dicarboxylic acid obtained by degradation of tetrahydrohumulene (Clemo and Harris, *J.*, 1952, 665). The identity is confirmed by cyclisation to the acyloins and oxidation to the same 4 : 8 : 8 : 11- or 3 : 7 : 7 : 10-tetramethyl*cyclo*undecane-1 : 2-dione.

These experiments show the structure of humulene to be based on a 1 : 4 : 4 : 8-tetramethyl*cyclo*undecane skeleton.

The preparation of 2 : 6 : 6 : 9-tetramethyldecane-1 : 10-dioic, 2 : 5 : 5-trimethyloctane-1 : 8-dioic, and 4 : 4-dimethyloctane-1 : 8-dioic acids is also described.

Humulene (α-caryophyllene), on degradative evidence, has been provisionally formulated as a 1 : 4 : 4 : 8-tetramethyl*cyclo*undecatriene (I) (Clemo and Harris, *J.*, 1951, **22**; 1952, 665; Harris, *J.*, 1953, 184) directly derivable from the established structure of β-caryophyllene. This structure and an alternative (II) based on 1 : 3 : 3 : 8-tetramethyl*cyclo*undecane, not so related to β-caryophyllene, have also been proposed by Šorm, Streibl, Pliva, and Herout (*Chem. Listy*, 1951, **45**, 308; 1953, **46**, 30).


(I)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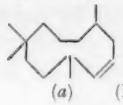

(*a*) (III) (*b*)

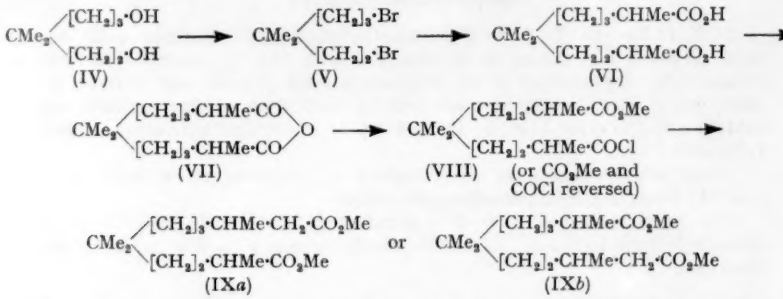
The trimethylammonium iodide from hexahydrohumulene, prepared by the catalytic hydrogenation of humulene nitrosochloride with subsequent methylation and quaternization, gives on Hofman degradation a monounsaturated tetrahydrohumulene; this on ozonolysis yields a C_{15} dibasic acid (Clemo and Harris, *loc. cit.*, 1952). Tetrahydrohumulene is most readily formulated as (III*a* or *b*) which would give 3 : 7 : 7 : 10- or 2 : 6 : 6 : 9-tetramethylundecane-1 : 11-dioic acid under these conditions. In order to confirm the presence of this unique ring system in the phytochemical pattern, and to reach a decision on the precise position of the alkyl group, the synthesis of a suitable tetramethylundecanedioic acid was undertaken by the annexed route.

The first steps are self-explanatory. When the dimethyl ester from the acid (VI) was fractionated, one main fraction was obtained; there being no evidence for the presence of a second isomer this fraction was hydrolysed. The acid, further purified by distillation, was obtained as a viscous oil, characterised as its bis-*p*-bromobenzylthiuronium salt, m. p. 140°, and was converted into the cyclic anhydride (VII), which with one equivalent of sodium methoxide gave the salt of an acid ester. The corresponding free acid ester was converted into the ester-chloride (VIII) and then homologized by the Arndt–Eistert procedure to the diester (IX*a* or *b*). Chromatography of the derived dicarboxylic acid gave a viscous oil which yielded a crystalline bis-*p*-bromobenzylthiuronium salt undepressed in m. p. by the compound obtained from the C_{15} degradation acid from natural sources. The methyl esters of the natural and the synthetic acid showed identical infra-red spectra from 5 to 14 μ but there was little resolution in the main finger-print region (9—14 μ).

To confirm the identity of these acids, both the natural and the synthetic ester were cyclized to the acyloins. These unsolidifiable oils were oxidized directly to the corresponding α-diketones with chromic acid. The infra-red absorption spectra showed identity of positions of all the bands but differences of strength for some of them. It may be assumed that the diketones were mixtures of stereoisomers in different proportions which

* Part III, *J.*, 1953, 184.

may arise (with slight variations in experimental conditions) from the molecules possessing enolizable asymmetric centres, and/or to a difference in the keto–enol ratio, for which there is support in the difference in intensity of the OH band at 3500 cm.$^{-1}$. However, the same 2 : 4-dinitrophenylosazone was obtained from both diketones.


CMe2 [CH2]3·OH [CH2]2·OH (IV)
CMe2 [CH2]3·Br [CH2]2·Br (V)
CMe2 [CH2]3·CHMe·CO2H [CH2]2·CHMe·CO2H (VI)
CMe2 [CH2]3·CHMe·CO [CH2]2·CHMe·CO O (VII)
CMe2 [CH2]3·CHMe·CO2Me [CH2]2·CHMe·COCl (VIII) (or CO2Me and COCl reversed)
CMe2 [CH2]3·CHMe·CH2·CO2Me [CH2]2·CHMe·CO2Me (IXa)
or
CMe2 [CH2]3·CHMe·CO2Me [CH2]2·CHMe·CH2·CO2Me (IXb)

From the above method of preparation it is not possible to decide whether the C_{15} acid is 3 : 7 : 7 : 10- or 2 : 6 : 6 : 9-tetramethylundecane-1 : 11-dioic acid. However, either structure confirms humulene as an eleven-membered cyclic hydrocarbon derived from 1 : 4 : 4 : 8-tetramethyl*cyclo*undecane and eliminates formula (II).

In connection with these syntheses 2 : 5 : 5-trimethyl- and 4 : 4-dimethyl-octane-1 : 8-dioic acids were prepared : the former from 3 : 3-dimethylpentane-1 : 5-diol by conversion into the dibromide, followed by consecutive condensations with one equivalent each of methylmalonic ester and potassium cyanide and hydrolysis; and the latter from 1 : 6-dibromo-3 : 3-dimethylhexane *via* the dinitrile, with final hydrolysis.

Experimental

Infra-red absorption spectra were measured on a Grubb-Parsons single-beam spectrometer on liquid films of 0·02 mm. thickness between sodium chloride plates.

3 : 3-*Dimethylhexane*-1 : 6-*diol*.—Diethyl ββ-dimethyladipate (30·5 g.) in dry ether (30 c.c.) was reduced with lithium aluminium hydride (350 c.c. of 100-vol. ethereal solution *), added gradually with stirring. Excess of reagent was destroyed by water and 10% sulphuric acid (300 c.c.), the aqueous layer was further extracted with ether, the combined extracts were dried (Na_2SO_4), the solvent was removed, and the residue distilled. The slightly turbid distillate was clarified by shaking it with a little benzene, separated, and redistilled, to give 3 : 3-*dimethylhexane*-1 : 6-*diol* as a viscous liquid (17·5 g., 90%), b. p. 116—118°/2 mm. (Found : C, 66·0; H, 12·3. $C_8H_{18}O_2$ requires C, 65·8; H, 12·3%).

1 : 6-*Dibromo*-3 : 3-*dimethylhexane*.—3 : 3-Dimethylhexane-1 : 6-diol (18·0 g.) was heated at 120—130° and saturated with dry hydrogen bromide. The product was extracted with ether, the ethereal solution washed with dilute sodium hydrogen carbonate solution and then water and dried (Na_2SO_4), and the solvent removed. The residue was distilled, to give the *dibromide* (23·8 g., 71%), b. p. 92—94°/2 mm. (Found : C, 35·9; H, 6·1. $C_8H_{16}Br_2$ requires C, 35·3; H, 5·9%).

Tetraethyl 1 : 6 : 6 : 9-*Tetramethyldecane*-1 : 1 : 10 : 10-*tetraoate*.—A solution of sodium (5·58 g.) in absolute alcohol (187 c.c.) was added during 1½ hr. to a mixture of 1 : 6-dibromo-3 : 3-dimethylhexane (33 g.) and diethyl methylmalonate (63·5 g., 3 equivs.) with stirring at 110°, and kept thereat for 12 hr. The mixture was cooled, the sodium bromide dissolved in water, and the *ester* separated with ether, dried (Na_2SO_4), and distilled as a colourless liquid (38·0 g., 50%), b. p. 162—6°/0·3 mm. (Found : C, 62·9; H, 9·3. $C_{24}H_{42}O_8$ requires C, 62·9; H, 9·2%).

Dimethyl 2 : 6 : 6 : 9-*Tetramethyldecane*-1 : 10-*dioate*.—The above ester (38·0 g.) was hydrolysed by refluxing methanolic potassium hydroxide (35%; 175 c.c.). The solution was acidified, the free acid extracted with ether and dried (Na_2SO_4), and the solvent removed. The crude acid was then decarboxylated at 130—170° for 3 hr. in the presence of glass wool. The crude acid was converted into the dimethyl ester with an excess of ethereal diazomethane. The

* This expression refers to the number of volumes of hydrogen liberated by 1 volume of ethereal solution.

crude product was slowly fractionated and *dimethyl* **2 : 6 : 6 : 9-***tetramethyldecane*-**1 : 10-***dioate* distilled as a colourless liquid (16 g., 62% calc. from the tetracarboxylic ester), b. p. 113—6°/0·5 mm. (Found : C, 67·4; H, 10·6. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·5%).

2 : 6 : 6 : 9-*Tetramethyldecane*-**1 : 10-***dioic Acid*.—The above ester (16·0 g.) was refluxed overnight in methanolic potassium hydroxide (35%; 50 c.c.). The methanol was removed and after acidification the free acid was extracted with sodium carbonate solution. Distillation of the product gave **2 : 6 : 6 : 9-***tetramethyldecane*-**1 : 10-***dioic acid* as a colourless viscous gum (14·0 g., 95%), b. p. 95—105° (bath-temp.)/0·001 mm. (Found : C, 65·2; H, 10·4. $C_{15}H_{26}O_4$ requires C, 65·1; H, 10·1%). The p-*bromobenzylthiuronium* salt formed colourless needles (from acetone), m. p. 140° (Found : C, 48·4; H, 6·2. $C_{31}H_{46}O_4N_4Br_2S_2$ requires C, 48·1; H, 5·9%).

2 : 6 : 6 : 9-*Tetramethyldecane*-**1 : 10-***dioic Anhydride*.—The dicarboxylic acid (14 g.) was heated (1 hr.) with acetic anhydride (14 g.) at 135°. The temperature was raised so that the acetic acid and excess of acetic anhydride slowly distilled off. The last traces of acetic anhydride were removed at the water-pump, and the residual *anhydride* distilled as a viscous oil which partially solidified (12·5 g., 96%), b. p. 100° (bath-temp.)/0·001 mm. (Found : C, 70·2; H, 10·2. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·0%).

9-*Methoxycarbonyl*-**2 : 5 : 5 : 9-** *or* **-2 : 6 : 6 : 9-***tetramethylnonan*-**1-***oic Acid*.—**2 : 6 : 6 : 9**-Tetramethyldecane-**1 : 10**-dioic anhydride (12·5 g.) in dry ether (20 c.c.) was refluxed with a solution from sodium (1·195 g.) in absolute methanol (40 c.c.) (1 hr.). The methanol was removed, the residue dissolved in dilute sodium carbonate solution, the neutral material extracted with ether, and the acid ester extracted (after acidification) with ether, dried (Na_2SO_4), and fractionated. Two fractions were obtained : (i) acid ester (6·9 g.), b. p. 147—50°/0·4 mm. (Found : equiv., 261) and (ii) dibasic acid (with some unchanged anhydride) (4·0 g.), b. p. 146—168°/0·2 mm. (Found : equiv., 180). From the sodium carbonate extract dimethyl ester was recovered (2·8 g.). This material was combined with fraction (ii), hydrolysed with alcoholic potassium hydroxide, converted into the anhydride, and reopened to the acid ester. Total yield of *acid ester* was 9·2 g. (65%) (Found : C, 66·3; H, 10·2. $C_{15}H_{28}O_4$ requires C, 66·2; H, 10·3%).

9-*Methoxycarbonyl*-**2 : 6 : 6 : 9-***tetramethylnonan*-**1-***oyl Chloride* (*or its Isomer*).—The above acid ester (9·2 g.) and thionyl chloride (4·5 g.) were warmed at 40° until the evolution of hydrogen chloride subsided. The temperature was gradually raised and the mixture refluxed (30 min.). Excess of thionyl chloride was removed at the water-pump, and the residue distilled. The *ester-chloride* was a colourless liquid which gradually darkened and had b. p. 102·5°/0·3 mm. (8·0 g., 81%) (Found : C, 62·3; H, 9·7. $C_{15}H_{27}O_3Cl$ requires C, 62·0; H, 9·3%).

2 : 6 : 6 : 9- *or* **3 : 7 : 7 : 10-***Tetramethylundecane*-**1 : 11-***dioic Acid*.—The ester chloride (8·0 g.) was added with stirring to an ethereal diazomethane solution containing twice the theoretical amount of diazomethane and set aside for 1 hr. The ether and excess of diazomethane were removed below 25° and the diazo-ketone dissolved in methanol (20 c.c.) at 0°. This solution was heated at 60° and the diazoketone decomposed by the addition of small portions of silver oxide, added at intervals, until the evolution of nitrogen ceased. The solution was refluxed for 1 hr. further, then filtered, and the methanol was removed from the filtrate. The residue was fractionated and the fraction (3·8 g., 48%), b. p. 102·7°/0·1 mm., collected (Found : C, 68·0; H, 11·0. $C_{17}H_{32}O_4$ requires C, 68·0; H, 10·7%). A sample of the *dimethyl* ester (500 mg.) was hydrolysed in methanolic potassium hydroxide (35%; 15 c.c.), and the free acid purified by chromatography on a silica column with subsequent elution with benzene–light petroleum (b. p. 60—80°) (1 : 2). **2 : 6 : 6 : 9-** or **3 : 7 : 7 : 10-***Tetramethylundecane*-**1 : 11-***dioic acid* (400 mg.), obtained by distillation after removal of the solvent, had b. p. 175° (bath-temp.)/0·001 mm. It remained a colourless gum (Found : C, 66·5; H, 10·5. $C_{15}H_{28}O_4$ requires C, 66·2; H, 10·3%). The *bis*-p-*bromobenzylthiuronium* salt recrystallised from acetone as colourless plates, m. p. 160·5° (Found : C, 49·1; H, 5·8. $C_{31}H_{46}O_4N_4$ requires C, 48·8; H, 6·0%). This was not depressed on admixture with the bis-*p*-bromobenzylthiuronium salt from the natural C_{15} acid (Clemo and Harris, *loc. cit.*). The acid recovered from this salt was converted into the dimethyl ester with diazomethane, and the infra-red absorption recorded; bands occur at 1739, 1587, 1429, 1341, 1250, 1183, 1149, 1075, and 1005 cm.$^{-1}$.

3 : 6 : 6 : 10- *or* **3 : 7 : 7 : 10-***Tetramethylcycloundecane*-**1 : 2-***dione*.—Sodium (1·2 g.) and purified xylene (150 c.c.) were heated in a current of pure dry nitrogen with high-speed stirring. After the sodium had been finely dispersed dimethyl **2 : 6 : 6 : 9-** or **3 : 7 : 7 : 10**-tetramethylundecane-**1 : 11**-dioate was added during 15 min. Stirring and heating were continued for a further 15 min., the mixture was cooled to 0°, and the sodium salts were decomposed by the

slow addition (at <30°) of methanol (50 c.c.). The xylene layer was washed with water until neutral, then dried (Na_2SO_4), the solvent removed at the water-pump, the residue fractionated, and a crude acyloin fraction (0·5 g., 24%), b. p. 125—140° (bath-temp.)/0·6 mm., collected.

The acyloin fraction, in acetic acid (2 c.c.), was added slowly with stirring to a solution of chromic anhydride (0·2 g.) in water (1 c.c.) and acetic acid (2 c.c.) cooled in ice–salt. The mixture was allowed to come to room temperature overnight. The diketone was extracted with ether, the extract was neutralised with dilute sodium carbonate solution, washed with water, and dried (Na_2SO_4), the solvent removed, and the residue distilled. The **3 : 6 : 6 : 10-** or **3 : 7 : 7 : 10-*tetramethylcycloundecane*-1 : 2-*dione*** (0·17 g., 35%), b. p. 90—110° (bath-temp.)/0·3 mm., distilled as a bright yellow liquid (Found: C, 76·0; H, 11·1. $C_{15}H_{26}O_2$ requires C, 75·7; H, 10·9%). Infra-red absorption bands were observed at 3500, 3008, 1720, 1470, 1302, 1254, 1170, 1087, 1044, 1007, 975, 947, 932, 919, 906, 863, 782, 756, and 740 cm.$^{-1}$.

The diketone gave, with 2 : 4-dinitrophenylhydrazine in alcohol solution on the boiling-water bath, a red amorphous uncrystallizable precipitate. The decanted supernatant liquor on cooling gave a solid ***bis*-2 : 4-*dinitrophenylhydrazone*** which recrystallised from ethyl acetate as needles, m. p. 231° (Found: C, 54·5; H, 6·0. $C_{23}H_{26}O_8N_8$ requires C, 54·2; H, 5·7%).

The C_{15} dibasic acid (Clemo and Harris, *loc. cit.*) was esterified with diazomethane, to give a colourless ester, b. p. 106—10°/0·1 mm., the infra-red absorption spectrum of which was identical with that of the synthetic ester. This ester was cyclised as above. The crude acyloin fraction (0·4 g., 20%) distilled over the range 90—120°/0·3 mm. This was oxidized, as previously described, to the bright yellow **3 : 6 : 6 : 10-** or **3 : 7 : 7 : 10-tetramethyl*cyclo*undecane-1 : 2-dione** (0·21 g., 53%), b. p. 90—115° (bath-temp.)/0·3 mm. (Found: C, 75·9; H, 11·1%). The infra-red absorption bands were all at the positions recorded for the synthetic product. This material gave with 2 : 4-dinitrophenylhydrazine a bis-2 : 4-dinitrophenylhydrazone, which crystallised from ethyl acetate as needles, m. p. alone or mixed the similar compound above, 231° (Found: C, 54·5; H, 6·0%).

1 : 5-*Dibromo*-3 : 3-*dimethylpentane*.—3 : 3-Dimethylpentane-1 : 5-diol (6·0 g.), from the lithium aluminium hydride reduction of diethyl ββ-dimethylglutarate, was brominated as described above for the dibromohexane. **1 : 5-*Dibromo*-3 : 3-*dimethylpentane*** distilled as a colourless liquid which gradually darkened (3·9 g., 33%), b. p. 82·4°/3 mm., n_D^{25} 1·5059 (Found: C, 32·9; H, 5·7. $C_7H_{14}Br_2$ requires C, 32·0; H, 5·5%). Similar yields were obtained on bromination with phosphorus tri- and penta-bromide.

Diethyl* 7-*Bromo*-5 : 5-*dimethylheptane*-2 : 2-*dicarboxylate.—A solution from sodium (0·32 g.) in absolute alcohol (10·6 c.c.) was added with stirring during 1 hr. to a mixture of **1 : 5-dibromo-3 : 3-dimethylpentane** (6·9 g.) and diethyl methylmalonate (2·35 g., 1 equiv.) at 100° and the temperature maintained for a further 2 hr. The mixture was cooled, water added, and the bromo-ester separated with ether and dried (Na_2SO_4). The solvent was removed and the residue fractionated to give (i) recovered diethyl methylmalonate (2 g.), (ii) recovered dibromide (3 g.), and (iii) the required ***bromo-ester*** (1·1 g.), b. p. 99—101°/0·1 mm. (Found: C, 51·7; H, 7·3. $C_{15}H_{27}O_4Br$ requires C, 51·3; H, 7·7%).

2 : 5 : 5-*Trimethyloctane*-1 : 8-*dioic Acid*.—The above bromo-ester (7·0 g.) was refluxed (24 hr.) with potassium cyanide (3·8 g.) in absolute alcohol (100 c.c.). The alcohol was removed and the nitrile extracted with ether.

The residue after evaporation of the ether was hydrolysed by refluxing alcoholic potassium hydroxide (20%, 50 c.c.) for 48 hr. The alcohol was removed, the residue acidified, and the acid isolated through sodium carbonate solution and dried (Na_2SO_4). The solvent was removed and the product distilled at 140—160°/0·001 mm. **2 : 5 : 5-*Trimethyloctane*-1 : 8-*dioic acid*** was obtained as a colourless gum, which solidified in the refrigerator (m. p. 41°; 1·8 g., 38%), b. p. 130—140° (bath-temp.)/0·001 mm. (Found: C, 61·2; H, 9·3. $C_{11}H_{20}O_4$ requires C, 61·2; H, 9·3%). The ***di*-p-*phenylphenacyl*** ester crystallised as needles (from ethanol), m. p. 110° (Found: C, 77·3; H, 6·9. $C_{39}H_{40}O_6$ requires C, 77·5; H, 6·6%).

1 : 6-*Dicyano*-3 : 3-*dimethylhexane*.—**1 : 6-Dibromo-3 : 3-dimethylhexane** (4·0 g.) was refluxed (60 hr.) with potassium cyanide (2·3 g.) in alcohol (15 c.c.) and water (2 c.c.). The alcohol was removed, the residue extracted with ether and dried (Na_2SO_4), and the solvent removed. The ***dinitrile*** distilled as a colourless liquid (1·6 g., 66%), b. p. 148—151°/3 mm. (Found: C, 73·0; H, 10·0. $C_{10}H_{16}N_2$ requires C, 73·2; H, 9·8%).

4 : 4-*Dimethyloctane*-1 : 8-*dioic Acid*.—The dinitrile was heated at 150° with potassium hydroxide (0·5 g.) in alcohol (2 c.c.). Water was added, the mixture acidified, the acid extracted through sodium carbonate solution, and the solvent removed. The residue was distilled in a high vacuum and the gum obtained purified on a silica column with elution with benzene–

chloroform (1 : 1). 4 : 4-*Dimethyloctane*-1 : 8-*dioic acid* redistilled as a colourless gum which solidified in the refrigerator (0·4 g., 54%), b. p. 140—160° (bath-temp.)/0·001 mm. (Found : C, 59·3; H, 8·7. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%). The acid was characterised as its *bis*-p-*bromobenzylthiuronium* salt, m. p. 155° (Found : C, 44·8; H, 5·29. $C_{26}H_{36}O_4N_4S_2Br_2$ requires C, 45·0; H, 5·2%), and as its *di*-p-*phenylphenacyl* ester, m. p. 36° (Found : C, 77·6; H, 6·7. $C_{38}H_{38}O_6$ requires C, 77·3; H, 6·45%).

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*The Chemistry of Humulene. Part V.**

By R. W. FAWCETT and J. O. HARRIS.

[Reprint Order No. 5134.]

*cyclo*Nona-1 : 3-diene, *cyclo*deca-1 : 3-diene, and *cyclo*undeca-1 : 3-diene have been prepared from the corresponding monoenes. The ultra-violet absorption maxima and refractive indices of these substances show a marked correlation with ring size. Infra-red absorption spectra are also recorded.

Comparison of the chemical and physical properties of these compounds with those of humulene confirms the absence of conjugation in the latter. This, together with the original and newer degradative and spectral evidence, leads to the most probable formation of humulene as 2 : 6 : 6-trimethyl-9-methylene*cyclo*undeca-1 : 4-diene (III*a*) or 2 : 5 : 5-trimethyl-9-methylene-*cyclo*undeca-1 : 6-diene (V).

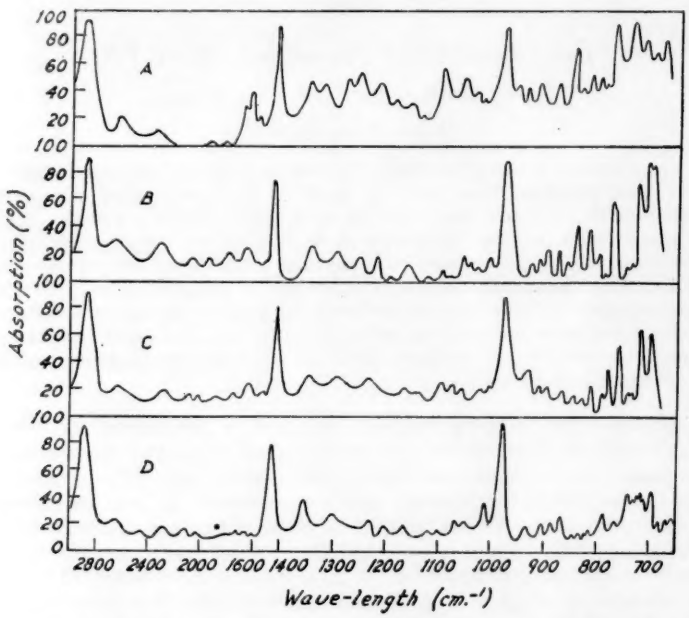
THE structure of the sesquiterpene humulene as a 1 : 4 : 4 : 8-tetramethyl*cyclo*undecatriene has been indicated by degradative and synthetic evidence, and from consideration of physical constants (for references see Fawcett and Harris, Part IV *). The exact arrangement of the double bonds has however not been deduced. It was considered from the absence of absorption above 2300 Å, and the failure to obtain a maleic anhydride adduct or to reduce humulene with sodium and alcohol, that the natural hydrocarbon was unconjugated. Pesch and Friess's observation (*J. Amer. Chem. Soc.*, 1950, **72**, 5756) that the ultra-violet absorption maxima of *cyclo*hepta- and *cyclo*octa-1 : 3-dienes occur at shorter wave-lengths than that of *cyclo*hexa-1 : 3-diene, but absence of information regarding the hitherto undescribed nine-, ten-, and eleven-membered ring compounds, rendered the ultra-violet absorption measurements inconclusive. Similarly the inability to form a maleic anhydride adduct from *cyclo*octa-1 : 3-diene (Cope and Estes, *ibid.*, 1950, **72**, 1128; Ziegler and Wilms, *Annalen*, 1950, **567**, 1) and lack of experimental evidence for the immediately higher ring homologues made further information desirable. So *cyclo*nona-, *cyclo*deca-, and *cyclo*undeca-1 : 3-diene have been prepared, all as colourless liquids by allylic bromination of the corresponding *trans*-monoenes with *N*-bromosuccinimide followed by dehydrohalogenation with quinoline. *cyclo*Deca-1 : 3-diene was also prepared by Hofmann degradation of *cyclo*undec-2-enyltrimethylammonium iodide and, after purification, was identical (infra-red spectrum) with the sample obtained by the alternative method. The conjugated dienes were purified by chromatography on alumina. All three showed marked absorption (see Fig. 1) at 975 cm.$^{-1}$, characteristic of a *trans*-disecondary olefinic linkage. They therefore possess a *cis-trans*-configuration, since a *trans-trans*-arrangement can only be accommodated, on Stuart models, for *cyclo*dodeca-1 : 3-diene and higher homologues. However, the infra-red absorption pattern in the 950—1020 cm.$^{-1}$ region in all cases resembles more closely that recently associated with a *trans-trans*-configuration in aliphatic compounds—for *cis-trans*-compounds bands of similar intensity occur at 950, 985, and 1020

* Part IV, preceding paper.

cm.$^{-1}$ (Celmer and Solomons, *J. Amer. Chem. Soc.*, 1953, **75**, 1372), for the presence of which there is some indication also in *cis-trans-cyclo*octa-1 : 3-diene (cf. Cope and Estes, *loc. cit.*). A definite decision on the stereoisomeric form of these new dienes is therefore not possible.

*cyclo*Undecene, not previously described, was prepared by dehydration of *cyclo*undecanol with phthalic anhydride. This leads to a mixture of *cis*- and *trans-cyclo*nonenes from *cyclo*nonanol, in which case Stuart models show the *cis*-form to be less strained, whereas in the case of *cyclo*decanol where models show both *cis*- and *trans-cyclo*decene to be strainless only the *trans*-isomer is formed. Hence it may be assumed that in this preparation of *cyclo*undecene, where both geometric isomers are also equally strainless, the *trans*-isomer is also produced. This is confirmed by the marked absorption at 975 cm.$^{-1}$.

FIG. 1.



Ultra-violet absorption spectra for : A, cyclo*nona*-1 : 3-*diene ; B*, cyclo*deca*-1 : 3-*diene ; C*, cyclo*undeca*-1 : 3-*diene ; D*, trans-cyclo*undecene*.

The hitherto undescribed *cyclo*undecane-1 : 2-dione was also prepared by the chromic acid oxidation of the corresponding acyloin, and characterised.

The undecane-1 : 11-dioic acid required for this synthesis was prepared by Sauer's method (*ibid.*, 1947, **69**, 2444) from δ-ethoxyvaleryl chloride. Also, undecylenic ester epoxide (Lévy and Willisch, *Bull. Soc. chim.*, 1929, **45**, 930) on catalytic hydrogenation over Raney nickel at 156°/60 atm. gave a mixture of 11- and 10-hydroxyundecanoic acid, in which the former predominated. Oxidation of this mixture gave the required undecane-1 : 11-dioic acid and 10-oxoundecanoic acid, which were readily separated.

Attempts to obtain an adduct with maleic anhydride and *cyclo*nona-, *cyclo*deca-, or *cyclo*undeca-1 : 3-diene were abortive. In the possible Stuart models of the *cis-trans*-configurations, whilst all three dienes can assume a "*cisoid*"-form (cf. Alder and Schumacher, *Annalen*, 1950, **571**, 81), the adducts are all strained, this being least in the C_{11} compound. It may be noted that, although *cyclo*dodeca-1 : 3-diene forms a liquid adduct with maleic anhydride, this cannot be dehydrogenated but redissociates on pyrolysis (Bartlett, Figdor, and Wiesner, *Canad. J. Chem.*, 1952, **30**, 291).

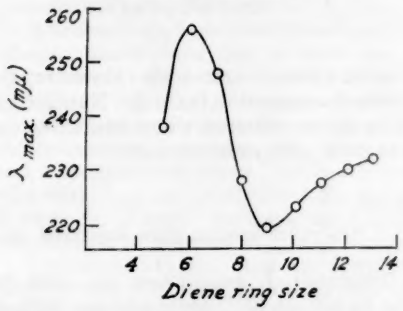
From these observations coupled with that of Cope and Estes (*loc. cit.*), this reaction

cannot be taken as a criterion for the presence of a conjugated *endo-endo*-system in C_{8-11} cyclic dienes.

The ultra-violet absorption measurements on the dienes showed that the smallest value for the maximum was reached at the C_9 compound ($\lambda_{max.}$ 2195 Å) (Figs. 2 and 3). *cyclo*-Undeca-1 : 3-diene has $\lambda_{max.}$ 2275 Å, and a pure sample of humulene showed a maximum of 2155 Å. This therefore appears to exclude the presence of an *endo-endo*-conjugated diene grouping in humulene in which the additional alkyl groups would be expected to produce a bathochromic shift.

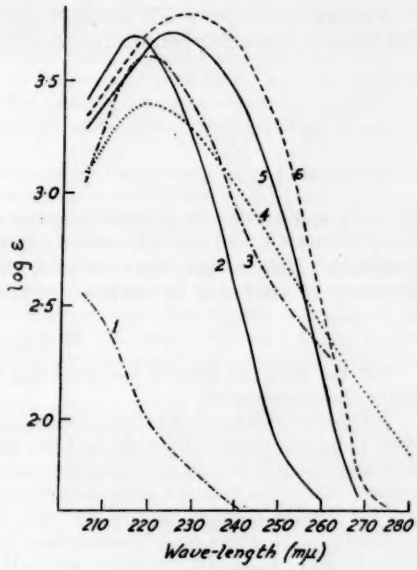
The refractive indices also show a minimum value at *cyclo*nona-1 : 3-diene.

FIG. 2. *Effect of ring-size on ultra-violet absorption maxima.*



References: 1, Pesch and Friess, *J. Amer. Chem. Soc.*, 1950, **72**, 5756; 2, Bartlett, Figdor, and Wiesner, *Canad. J. Chem.*, 1952, **30**, 291); 3, Ingraham, MacDonald, and Wiesner, *Canad. J. Res.*, 1950, **28**, *B*, 453.

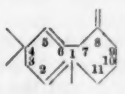
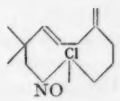
FIG. 3.



Ultra-violet absorption spectra: 1, cyclo*undecene*; 2, *humulene*; 3, *dihydrohumulene*; 4, cyclo*nona*-1 : 3-*diene*; 5, cyclo*deca*-1 : 3-*diene*; 6, cyclo*undeca*-1 : 3-*diene*.

The fact that *cyclo*deca- and *cyclo*undeca-1 : 3-diene undergo normal reduction to the corresponding monoenes with sodium and alcohol also supports the absence of conjugation in humulene.

Structure (I) is the only formula, based upon a 1 : 4 : 4 : 8-*cyclo*undecane skeleton, in which a precise designation of the double bonds of humulene has been given (Šorm, Streibl,

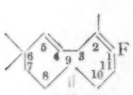
(I)   (II)

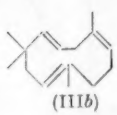
Pliva, and Herout, *Chem. Listy*, 1951, **45**, 308; 1953, **46**, 30). Consideration of all the possible trebly unsaturated structures which may be based on this skeleton leads to 5 : 6 as the best position for the R·CH:CH·R system, the presence of which is clearly shown by the absorption at 975 cm.$^{-1}$ (Šorm, *Coll. Czech. Chem. Comm.*, 1949, **14**, 718). No other position leads to a non-conjugated structure which accounts readily for αα-dimethylsuccinic acid and lævulaldehyde as the first products of ozonolysis (Clemo and Harris, *loc. cit.*). The nitrosochloride is probably formed at the endocyclic disubstituted olefinic linkage. This is supported by the strong absorption at 980 cm.$^{-1}$ in this derivative indicative of the presence

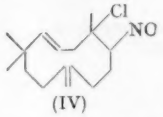
still of R·CH:CH·R; and absorption at 890 cm.$^{-1}$ shows the retention of the CH_2:CR_2 group also present in humulene. Presence of the exocyclic methylene group is confirmed in the nitrosochloride by the formation of formaldehyde on ozonolysis. Thus, on these grounds, formula (I) would lead to (II) as the structure of the nitrosochloride, which cannot readily accommodate all the degradative evidence, since reduction to the fully saturated amine followed by methylation, Hofmann degradation, and oxidation (Clemo and Harris, *J.*, 1952, 665) would not lead to a C_{15} acid of the established structure (preceding paper).

However the structure (III*a*) now suggested, with some co-existent endocyclic form (III*b*), whilst accounting satisfactorily for the products of ozonolysis and the spectral data would lead to (IV) as the formula of the nitrosochloride. This would give on the above degradation 2 : 6 : 6 : 9-tetramethylundecane-1 : 11-dioic acid, a permissible structure.

A unique structure which accounts directly for most of the degradative evidence is (V). This leads to the other permissible structure for the C_{15} degradation acid, and the lævul-


(III*a*)


(III*b*)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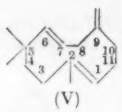
(V)

aldehyde could arise by decarboxylation of an intermediate β-keto-acid. However, the dimethylsuccinic acid can only arise if allylic oxidation is assumed to occur (cf. Ruzicka and Kaufmann, *Helv. Chim. Acta*, 1940, **23**, 1346). The choice between these structures can obviously be arrived at by the exact formulation of the C_{15} degradation acid.

Experimental

For the infra-red spectra see preceding paper. Ultra-violet spectra were measured on a Hilger Unispectrometer.

3-*Bromo*cyclo*decene*.—*trans-cyclo*Decene (4·5 g.) (Blomquist, *J. Amer. Chem. Soc.*, 1952, **74**, 3636) in carbon tetrachloride (22 c.c.) was heated for 45 min. at 100°, under nitrogen, with *N*-bromosuccinimide (5·8 g.) and benzoyl peroxide (50 mg.). The mixture was filtered, the filtrate washed with dilute sodium hydrogen carbonate solution and dried ($MgSO_4$), the solvent removed, and the residue distilled rapidly and then refractionated. 3-*Bromo*cyclo*decene* distilled as a colourless liquid which soon became dark red (4·0 g., 56%), b. p. 86—88°/2 mm. (Found : C, 55·6; H, 8·1. $C_{10}H_{17}Br$ requires C, 55·3; H, 7·8%).

cyclo*Deca*-1 : 3-*diene*.—(a) *By dehydrohalogenation.* 3-Bromo*cyclo*decene (4·0 g.) and quinoline (4·8 g.), both freshly distilled, were heated at 230° in a short-necked flask attached to a cooled receiver. The distillate (b. p. 165—185°) was washed with 5% hydrochloric acid (10 c.c.), extracted with ether, separated, and dried (Na_2SO_4); after removal of the solvent the *diene* distilled as a colourless, highly mobile liquid with a strong characteristic odour (2·2 g., 45%), b. p. 76—77°/14 mm. A sample, purified by chromatography on an alumina column, elution being with *n*-hexane, had n_D^{25} 1·4972, $\lambda_{max.}$ (in EtOH) 223 mμ (log ε 3·70) (Found : C, 88·4; H, 11·9. $C_{10}H_{16}$ requires C, 88·2; H, 11·8%). Quantitative hydrogenation over Adams catalyst in glacial acetic acid at room temperature and pressure confirmed the presence of two double bonds. With concentrated silver nitrate solution the diene forms a white addition compound, m. p. 176—178° (decomp.).

(b) *By Hofmann degradation.* 3-Bromo*cyclo*decene (8·5 g.) and dimethylamine (4·4 g.) in benzene (37 c.c.) were kept overnight; dimethylamine hydrobromide was filtered off, the filtrate was extracted with 10% hydrochloric acid (15 c.c.), and the extracts were warmed at 55—60° for 3—5 min. to hydrolyse any vinylamines present, and extracted with ether (15 c.c.). The aqueous solution was basified and extracted with ether; the extract was dried (Na_2SO_4) and evaporated, and distillation of the residue yielded colourless 3-*dimethylamino*cyclo*decene* (3·2 g., 45%), b. p. 88—90°/1 mm. (Found : C, 79·6; H, 13·0. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7%). The *picrate* recrystallised from alcohol in long fine needles, m. p. 158° (Found : C, 52·3; H, 6·5. $C_{18}H_{26}O_7N_4$ requires C, 52·7; H, 6·3%).

The base (3·1 g.) and methyl iodide (5·0 g.) in *cyclo*hexane (38 c.c.) were heated under reflux for 2½ hr. The quaternary *salt* was filtered off (4·8 g., 84%). A sample crystallised from ethanol had m. p. 205—208° (decomp.) (Found : C, 48·3; H, 8·5. $C_{13}H_{26}NI$ requires C, 48·3; H, 8·1%).

This salt (7·0 g.) was stirred for 2 hr. at room temperature with an excess of freshly prepared

silver oxide suspended in water (50 c.c.). The silver halide were filtered off, stirred with water (50 c.c.), and filtered off again, and the combined aqueous fractions (100 c.c.) were treated with solid sodium hydroxide (100 g.). The solution was heated under reflux for 1½ hr. The oil which separated was extracted with ether, dried (Na_2SO_4), and distilled. *cyclo*Deca-1 : 3-diene (2·2 g., 70%) was obtained as a colourless liquid, b. p. 89—91°/24 mm., n_D^{25} 1·4972 (Found : C, 88·1; H, 12·1%). This material, after chromatographic purification as described previously, was identical with the material obtained as above.

*cyclo*Deca-1 : 3-diene (250 mg.) and maleic anhydride (710 mg.) in dry xylene (20 c.c.) were refluxed overnight in an atmosphere of nitrogen. Removal of the solvent yielded only the unchanged starting materials.

Sodium and Alcohol Reduction.—*cyclo*Deca-1 : 3-diene (400 mg.) in absolute alcohol (10 c.c.) was heated under reflux, sodium (2·0 g.) was added in small portions during 30 min., and heating continued for 1 hr. The mixture was cooled, diluted with water, and extracted with ether, the extract was evaporated, and the residue shaken with 50% aqueous silver nitrate (0·5 c.c.). The solid from the unreduced diene was filtered off and washed with ether, and this ether was combined with the ether extract of the filtrate. The ethereal solutions were dried (Na_2SO_4) and concentrated, and the residue was distilled. Quantitative reduction of the product showed the presence of one double bond.

3-*Bromo*cyclo*nonene.*—*cyclo*Nonene (2·2 g.), prepared by the phthalic anhydride dehydration of *cyclo*nonanal (*idem, ibid.*, p. 3643) was brominated as described for *cyclo*decene. 3-*Bromo*cyclo*nonene* (1·6 g., 45%) distilled as a colourless liquid which gradually darkened (Found : C, 53·0; H, 7·4. $C_9H_{15}Br$ requires C, 53·2; H, 7·4%).

cyclo*Nona*-1 : 3-*diene.*—The foregoing bromide (1·5 g.) was dehalogenated as described for the *cyclo*decene derivative. The colourless *diene* (0·4 g., 42%) had b. p. 105—107°/170 mm., and a characteristic odour. After adsorption on alumina and elution with *n*-hexane it had n_D^{25} 1·4921, $\lambda_{max.}$ (in EtOH) 219·5 mμ (log ε 3·40) (Found : C, 88·7; H, 11·8. C_9H_{24} requires C, 88·5; H, 11·5%). Neither a maleic anhydride adduct nor an addition compound with silver nitrate could be prepared.

Undecane-1 : 11-*dioic Acid and Ethyl* 10-*Oxoundecanoate.*—Ethyl 10 : 11-epoxyundecanoate (10·0 g.) was catalytically reduced over Raney nickel (2 g.) in absolute alcohol (120 c.c.) at 150°/60 atm. until uptake of hydrogen ceased (3 hr.). The catalyst and alcohol were removed, the residue was distilled, and the distillate (8·0 g., 76%), b. p. 135—140°/0·8 mm., collected.

Chromic anhydride (8·7 g.) in concentrated sulphuric acid (4 c.c.) and water 40 c.c.) was added slowly at <25° with stirring to the hydroxy-ester (7·8 g.) in acetone (95 c.c.), and the mixture allowed to reach room temperature overnight. The acetone was removed under reduced pressure and the residue extracted with ether. The acidic products were extracted by sodium carbonate solution, then re-extracted after acidification into ether, the solvent was removed, and the residue was hydrolysed for 4 hr. with potassium hydroxide (5·2 g.) in water (25 c.c.). Acidification gave colourless undecane-1 : 11-dioic acid (5·0 g.), m. p. 101° undepressed on admixture with an authentic sample prepared by Sauer's method (*loc. cit.*) (Found : C, 61·3; H, 9·6. Calc. for $C_{11}H_{20}O_4$: C, 61·1; H, 9·3%).

The above ethereal extract of neutral oxidation products was dried (Na_2SO_4), the ether removed, and the neutral residue distilled, to give colourless ethyl 10-oxoundecanoate (1·3 g., 13%), b. p. 151—154°/5 mm. (Found : C, 68·7; H, 10·8. Calc. for $C_{13}H_{24}O_3$: C, 68·4; H, 10·5%). This yielded in alcohol the 2 : 4-*dinitrophenylhydrazone*, in orange needles, m. p. 65°, from alcohol (Found : C, 56·0; H, 7·0. $C_{19}H_{28}O_6N_4$ requires C, 55·9; H, 6·9%).

2-*Hydroxy*cyclo*undecanone.*—Diethyl undecane-1 : 11-dioate (53·0 g.) in xylene (400 c.c.) with sodium was cyclised by the acyloin procedure (cf. Blomquist, *loc. cit.*). A crude pale yellow acyloin fraction, b. p. 95—100°/0·4 mm., was obtained. 2-Hydroxy*cyclo*undecanone (12·5 g., 36%) was obtained pure by cooling a light petroleum (b. p. 40—60°) solution; it had m. p. 38° (Found : C, 71·7; H, 11·1. Calc. for $C_{11}H_{20}O_2$: C, 71·7; H, 10·9%).

cyclo*Undecanone.*—2-Hydroxy*cyclo*undecanone (10·7 g.), acetic acid (24 c.c.), zinc wool (24 g.), and concentrated hydrochloric acid (24 c.c.) were heated under reflux at 100—110°. Three similar quantities of hydrochloric acid were added at half-hourly intervals, after which heating was continued for 2 hr. The solution was filtered, diluted, and extracted with ether, the extract was washed with dilute sodium carbonate solution and then water and dried (Na_2SO_4), the ether removed, and the residue distilled. *cyclo*Undecanone (8·6 g., 88%) was obtained as a colourless liquid, b. p. 100—103°/2 mm. (Found : C, 78·5 : H, 12·0. Calc. for $C_{11}H_{20}$: C, 78·6; H, 11·9%).

cyclo*Undecanol.*—*cyclo*Undecanone (8·6 g.) in dry ether (10 c.c.) was added with stirring to

a solution of lithium aluminium hydride in ether (45 c.c., 100-vol.) * so that refluxing was just maintained. Excess of reagent was destroyed by water, and the complex decomposed with 10% sulphuric acid (65 c.c.). The ether layer, and ether extracts of the aqueous layer, were dried (Na_2SO_4), the solvent was removed, and the residue distilled. *cyclo*Undecanol (7·8 g., 91%) was obtained as a colourless viscous liquid, b. p. 79—82°/0·2 mm. (Found: C, 77·5; H, 13·2. Calc. for $C_{11}H_{22}O$: C, 77·7; H, 12·9%).

trans-cyclo*Undecene*.—*cyclo*Undecanol (7·7 g.) was added in portions to phthalic anhydride (16·0 g.), heated to b. p. in a Claisen flask with a refractionating column packed with carborundum lumps; when the addition was nearly complete the temperature was raised to 340°. The mixture of olefin and phthalic anhydride which distilled was warmed with 10% sodium hydroxide solution, cooled, and extracted with ether, the extract was dried (Na_2SO_4), the solvent removed, and the residue distilled. trans-cyclo*Undecene* (5·7 g., 80%) distilled as a colourless liquid, b. p. 116—119°/25 mm. Purified by chromatography on an alumina column and elution with hexane this had n_D^{25} 1·4802, $\lambda_{max.}$ (in EtOH) <200 mμ (Found: C, 87·0; H, 13·4. $C_{11}H_{20}$ requires C, 86·9; H, 13·1%).

3-*Bromo*cyclo*undecene*.—The above olefin (5·7 g.) was brominated as described for *cyclo*decene. 3-*Bromo*cyclo*undecene* (5·7 g., 66%) distilled as a colourless liquid, b. p. 116—119°/3 mm., which soon darkened (Found: C, 57·3; H, 8·6. $C_{11}H_{19}Br$ requires C, 57·2; H, 8·2%).

cyclo*Undeca*-1 : 3-*diene*.—The above bromide (5·7 g.) was dehalogenated as described for the *cyclo*deca-1 : 3-diene derivative. cyclo*Undeca*-1 : 3-*diene* (2·2 g., 59%) distilled as a highly mobile liquid with a characteristic odour, b. p. 107—109°/17 mm.; purified by chromatography on alumina and elution with *n*-hexane, it had n_D^{25} 1·5034, $\lambda_{max.}$ (in EtOH) 225 mμ (log ε 3·79) (Found: C, 87·8; H, 11·9. $C_{11}H_{18}$ requires C, 88·0; H, 12·0%). Quantitative hydrogenation over Adams catalyst in glacial acetic acid confirmed the presence of two double bonds. It gave with silver nitrate solution a white addition compound, m. p. 155° (decomp.), from which the diene was regenerated on shaking with a saturated solution. Attempts to make the maleic anhydride adduct, as described above, yielded only the starting materials. The diene was reduced by sodium and alcohol to *cyclo*undecene under conditions similar to those described above.

Ultra-violet Absorption of Humulene.—A sample of humulene (Clemo and Harris, *J.*, 1952, 22) was purified by chromatography on an alumina column and elution with *n*-hexane. A maximum at 215·5 mμ (log ε 3·69) in EtOH was observed.

Ozonolysis of Humulene Nitrosochloride.—Ozone was passed through a solution of humulene nitrosochloride (4·0 g.) in chloroform (50 c.c.) at 0°, to saturation. The solvent was removed under reduced pressure at <20° and the residue steam-distilled. The distillate, treated with dimedone solution, gave a solid which separated from alcohol as white needles, m. p. 189° alone or mixed with the dimedone formaldehyde compound. In Nujol mull in the 10—12 μ region, the pure nitrosochloride showed bands at 1018, 998, 980, 954, 942, 919, 910, 892, 870, 837, and 826 $cm.^{-1}$.

cyclo*Undecane*-1 : 2-*dione*.—2-Hydroxy*cyclo*undecanone (1·0 g.) in acetic acid (2 c.c.) was cooled and a cold solution of chromic anhydride (0·6 g.) in water (1 c.c.) and acetic acid (2·5 c.c.) was added slowly with stirring. Next morning saturated sodium chloride solution (5 c.c.) was added and the product extracted with ether. The extract was washed with dilute sodium carbonate solution and then water, dried (Na_2SO_4), and evaporated, and the residue was distilled. cyclo*Undecane*-1 : 2-*dione* (0·5 g., 50%) distilled as a bright yellow liquid, b. p. 87—90°/2 mm. (Found: C, 72·8; H, 10·3. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%). The red *bis*-2 : 4-*dinitrophenylhydrazone* had m. p. 285—286° (Found: C, 50·1; H, 5·0. $C_{23}H_{26}O_8N_8$ requires C, 50·9; H, 4·8%). The diketone in glacial acetic acid was warmed with *o*-phenylenediamine in alcohol, and the *quinoxaline* which separated recrystallised from alcohol as white needles, m. p. 145° (Found: C, 80·3; H, 9·0. $C_{17}H_{22}N_2$ requires C, 80·3; H, 8·7%).

The authors thank Professor G. R. Clemo, F.R.S., for his continued interest and King's College Council for the award of a Postgraduate Studentship (to R. W. F.).

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[*Received, February 17th*, 1954.]

* See footnote, p. 2670.

The Chemistry of Bacteria. Part III. An Indolylpyrrylmethene from Violacein.*

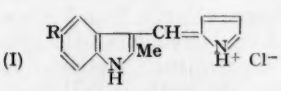
By R. J. S. Beer, B. E. Jennings, and Alexander Robertson.

[Reprint Order No. 5248.]

Degradation of acetylviolacein with hydriodic acid gives a yellow monoacidic base $C_{13}H_{10}O_2N_2$, which forms deep red salts and is believed to be a 5-hydroxyindolyl-hydroxypyrrylmethene. From the properties of synthetic model compounds, it appears that the C_{13} base is most probably a β-hydroxypyrrylmethene and it is inferred that this type of system is also present in violacein.

By thermal decomposition of violacein and oxidation of its acetyl derivative, conveniently termed acetylviolacein, it was shown that the violacein molecule contained a 5-hydroxyindole nucleus and an indole residue probably as oxindole (Part II *). From an examination of the product formed from acetylviolacein with hot hydriodic acid, it now appears that a hydroxypyrrole residue may also be present. This new degradation product, which was isolated as the deeply coloured, sparingly soluble hydriodide, is a yellow base, $C_{13}H_{10}O_2N_2$, best characterised as its red monohydrochloride and perchlorate. It formed a non-basic triacetyl derivative and, with methyl sulphate and alkali, yielded a monomethyl ether, $C_{13}H_9ON_2{\cdot}OMe$, which on acetylation furnished a diacetyl derivative and, like the parent base, gave rise to coloured salts. With aqueous sodium hydrogen carbonate, the base $C_{13}H_{10}O_2N_2$ formed an unstable sodio-derivative, readily decomposed with dilute acetic acid whilst an aqueous sodium hydroxide solution of the base soon became deep green, owing to aerial oxidation. With sodium dithionite (hydrosulphite) the green solution changed to red, reverting to green on aeration or treatment with hydrogen peroxide. In alkaline solution the methylated base was relatively stable to aerial oxidation.

From these results the product $C_{13}H_{10}O_2N_2$ appeared to be an indolylpyrrylmethene, a type of compound which apparently has not been described previously but which, by analogy with the well-known dipyrrylmethenes (pyrromethenes), would be expected to have properties similar to those exhibited by the base. The analytical data indicate that two hydroxyl groups are present and, from the results obtained in Part II (*loc. cit.*), it is reasonable to place one at the 5-position of the indole residue and the second in the pyrrole ring. To test this view an investigation on the preparation and properties of indolylpyrrylmethenes was initiated. Of the established methods for the synthesis of dipyrrylmethenes that which involved the condensation of a pyrrole-aldehyde with a second pyrrole residue appeared to be more generally applicable to the present case. Thus in some preliminary experiments the condensation of pyrrole-2-aldehyde with 2-methylindole by the action of alcoholic hydrogen chloride gave a deep red crystalline compound, presumably (I; R = H), which decomposed during the isolation process but which showed a similar ultra-violet absorption spectrum to the unstable product (I; R = OH) similarly obtained from 5-hydroxy-2-methylindole and the same aldehyde. In support of our hypothesis it was found



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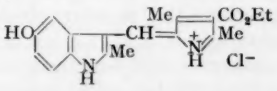


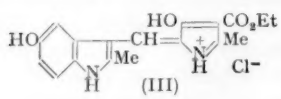
(II)

that the absorption curves of the synthetic products showed a definite resemblance to that of the hydrochloride of the base $C_{13}H_{10}O_2N_2$. With pyrrole-2-aldehyde and 3-methylindole only a dark amorphous insoluble product was formed. The methene hydrochloride (II) was readily formed from 3-ethoxycarbonyl-2 : 4-dimethylpyrrole and 5-hydroxy-2-methylindole-3-aldehyde, which was conveniently prepared from 5-hydroxy-2-methylindole by the Gattermann reaction. The salt (II) was unstable in hot solvents and could not be recrystallised but with pure reactants it was isolated analytically pure from the reaction mixture.

* Part II, *J.*, 1949, 885.

From the literature it appeared that, of the simple hydroxypyrroles and their aldehydes required for the synthesis of methenes of type (I) with a hydroxyl group in the pyrrole residue, the few known compounds were not readily accessible and therefore the more readily prepared ethoxycarbonyl derivatives of α- and β-hydroxypyrroles were employed in exploratory work. Thus 5-hydroxy-2-methylindole-3-aldehyde reacted smoothly with 3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole in cold alcoholic hydrogen chloride, giving the bright red 2′-(4′-ethoxycarbonyl-3′-hydroxy-5′-methylpyrryl)-3-(5-hydroxy-2-methylindolyl)-methene hydrochloride (III), the constitution of which was confirmed by its preparation from 5-hydroxy-2-methylindole and 4-ethoxycarbonyl-3-hydroxy-5-methylpyrrole-2-aldehyde. This compound resembled the salts of the C_{13} base from violacein in several respects, *e.g.*, it gave a sodio-derivative on treatment with aqueous sodium hydrogen carbonate, a monomethyl ether with methyl sulphate, and a yellow non-basic triacetyl derivative, solutions of which in pyridine, like those of the triacetyl derivative of the C_{13} base, showed a marked green fluorescence.

Attempts to condense 5-hydroxy-2-methylindole-3-aldehyde, with 2-hydroxy-, 4-ethoxycarbonyl-2-hydroxy-, or 3-ethoxycarbonyl-5-hydroxy-2-methyl-pyrrole by the same method were unsuccessful. No reaction occurred at room temperature and when the reaction mixtures were heated the product obtained in each case was 5 : 5′-dihydroxy-2 : 2′-dimethyldi-indolylmethene hydrochloride (IV) which was also formed from 5-hydroxy-2-methylindole and 5-hydroxy-2-methylindole-3-aldehyde in hot alcoholic hydrogen chloride or from 5-hydroxy-2-methylindole and formic acid.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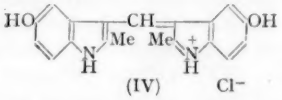
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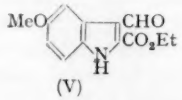
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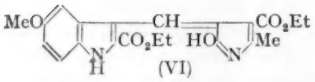
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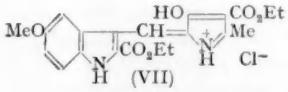
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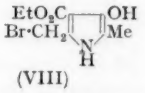
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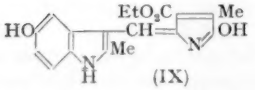
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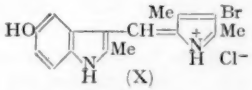
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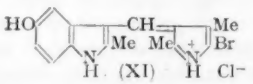
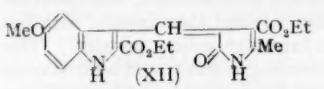
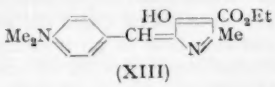

(XI)

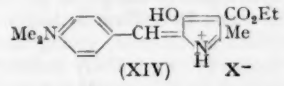
The α-hydroxypyrroles are obviously less reactive than 3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole and their failure to condense with 5-hydroxy-2-methylindole-3-aldehyde was attributed to the instability of the aldehyde in the hot reaction mixture. In attempting to overcome this difficulty 5-hydroxy-2-methylindole was heated with 4-ethoxycarbonyl-2-hydroxy-5-methylpyrrole-3-aldehyde but the di-indolylmethene (IV) was again formed, presumably by way of a di-indolylpyrrylmethene. That α-hydroxypyrroles are capable of reacting with indole-3-aldehydes in the desired manner was demonstrated by the successful preparation of 3′-(4′-ethoxycarbonyl-2′-hydroxy-5′-methylpyrryl)-3-(2-ethoxycarbonyl-5-methoxyindolyl)methene (VI) in warm alcoholic hydrogen chloride from 3-ethoxycarbonyl-5-hydroxy-2-methylpyrrole and 2-ethoxycarbonyl-5-methoxyindole-3-aldehyde (V), obtained from 2-ethoxycarbonyl-5-methoxyindole by Gattermann's method. As indicated by its separation from the hot acidic reaction mixture, the methene (VI) does not readily form salts and it does not react with aqueous sodium hydrogen carbonate. Prepared by the standard method from 3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole and isolated as the hydrochloride, the related β-hydroxypyrrylmethene (VII) is definitely basic and also forms a sodio-derivative. A further example of a weakly basic indolyl-α-hydroxypyrrylmethene is afforded by 2′-(3′-ethoxycarbonyl-5′-hydroxy-4′-methylpyrryl)-3-(5-hydroxy-2-methylindolyl)methene (IX) which was prepared by heating 2-bromomethyl-3-ethoxycarbonyl-5-hydroxy-4-methylpyrrole (VIII) with an excess of 5-hydroxy-2-methylindole in methanol, according to another known dipyrrylmethene synthesis (see, *e.g.*, Fischer and Alder, *Z. physiol. Chem.*, 1931, **197**, 246).

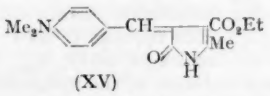
Certain hydroxypyrromethenes have been prepared from bromopyrromethenes by replacement of the nuclear bromine atoms with hydroxyl groups (cf. Lichenwald, *ibid.*, 1942, **273**, 118; Fischer and Reinecke, *ibid.*, 1939, **258**, 253). In an attempt to adapt this method, 2′-(4′-bromo-3′ : 5′-dimethylpyrryl)-3-(5-hydroxy-2-methylindolyl)- (X) and 3′-(5′-bromo-2′ : 4′-dimethylpyrryl)-3-(5-hydroxy-2-methylindolyl)-methene (XI) were synthesised by condensing 5-hydroxy-2-methylindole with 4-bromo-3 : 5-dimethylpyrrole-2- and 5-bromo-2 : 4-dimethylpyrrole-3-aldehyde respectively. Unfortunately the instability of these methenes in hot solvents precluded their use for the preparation of the corresponding hydroxy-compounds.

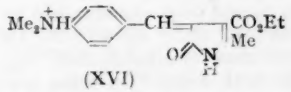
The remarkable difference in their degree of basicity serves to distinguish the two methenes (III) and VII) having a β-hydroxypyrrole residue from (VI) and (IX) with an α-hydroxypyrrole nucleus. Thus the methene hydrochlorides (III) and (VII) are relatively stable salts, whilst the methenes (VI) and (IX) separated as the free bases from acidic alcoholic solutions; this difference may be attributed to the existence of the α-hydroxypyrrole derivatives in the lactam form, *e.g.*, type (XII) (cf. Grob and Ankli, *Helv. Chim. Acta*, 1949, **32**, 2010; Davoll, *J.*, 1953, 3802). In this connexion the compounds (XIII) and (XV) formed by the condensation of *p*-dimethylaminobenzaldehyde with 3-ethoxycarbonyl-4-hydroxy-2-methyl- and 3-ethoxycarbonyl-5-hydroxy-2-methyl-pyrrole are of interest. Both products are yellow bases but, whereas (XIII) forms intensely violet salts, represented by the resonating ion (XIV), the α-hydroxypyrrole derivative (XV) gives only weakly coloured (orange) salts which are probably best represented by (XVI).


(XII)

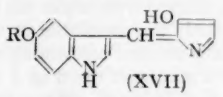

(XIII)

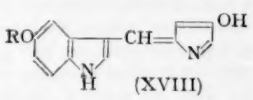

(XIV) X⁻

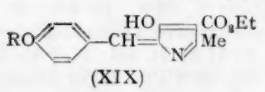

(XV)

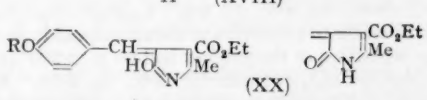

(XVI)

From the foregoing results it is clear that the properties of the C_{13} base from acetylviolacein are closely parallelled by those of the synthetic methene (III) and that the base does not contain an α-hydroxypyrrole residue. It therefore seems likely that the two probable structures for the C_{13} base are (XVII or XVIII; R = H) and hence the methyl ether of the base would be represented by (XVII or XVIII; R = Me) because on general


(XVII)


(XVIII)

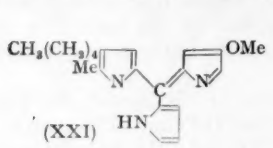

(XIX)

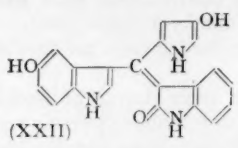

(XX)

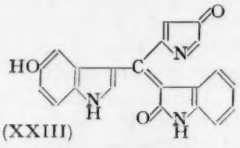
grounds the hydroxyl group in the indole residue would be expected to be preferentially methylated. It was found that in model methylation experiments with 2′-(4′-ethoxycarbonyl-3′-hydroxy-5′-methylpyrryl)- (XIX; R = H) and 3′-(4′-ethoxycarbonyl-2′-hydroxy-5′-methylpyrryl)-1-*p*-hydroxyphenylmethene (XX; R = H), only the hydroxyl groups in phenyl residues were alkylated. The orientation of the methylation products (XIX and XX; R = Me) was confirmed by the synthesis of these methenes from anisaldehyde and the requisite pyrroles.

The β-hydroxypyrrylmethene system in formulæ (XVII) and (XVIII) recalls the tripyrrylmethene structure (XXI) assigned to the bacterial pigment prodigiosin (Wrede and Rothhaas, *Z. physiol. Chem.*, 1934, **226**, 95) and the possibility that violacein may be a 5-hydroxyindolyl-hydroxypyrryl-oxindolylmethene [*e.g.*, type (XXII), $C_{21}H_{15}O_3N_3$ or an oxidised form of this, *e.g.*, (XXIII), $C_{21}H_{13}O_3N_3$] has not been overlooked. Structures of

this type, which are consistent with the results of oxidative degradations (unpublished work and Part II, *loc. cit.*), would account for the formation of 5-hydroxyindole and oxindole on pyrolysis and of an indolylpyrrylmethene, of type (XVII) or (XVIII), with hydriodic acid. On this basis the empirical formula $C_{42}H_{30}O_7N_6$ suggested by Wrede (see Part II, *loc. cit.*) for violacein could perhaps be accommodated by supposing the crystalline pigment


(XXI)


(XXII)


(XXIII)

to be a molecular complex of two C_{21} molecules, *e.g.*, $C_{21}H_{15}O_3N_3,C_{21}H_{13}O_3N_3,H_2O$, of the quinhydrone type but we prefer to reserve further discussion of possible structures until we have been able to interpret satisfactorily the results of other degradative work to be described in a later communication.

Experimental

Degradation of Acetylviolacein with Hydriodic Acid.—A mixture of acetylviolacein (Part II, *loc. cit.*) (0·2 g.), hydriodic acid (*d* 1·7; 10 ml.), and acetic acid (10 ml.) was heated under reflux (oil-bath at 130°) for 1½ hr. The resulting sparingly soluble, deep bronze, crystalline methene hydriodide (0·125 g.), m. p. >320°, which could not be satisfactorily recrystallised, was dissolved in warm 2N-sodium hydrogen carbonate (24 ml.), and the warm solution then treated with hot dilute acetic acid, giving the methene base as an insoluble brownish-yellow powder. This product (0·1 g.) slowly dissolved in boiling alcohol (30 ml.) containing concentrated hydrochloric acid (6 drops), giving a deep red solution which later deposited the *hydrochloride* in very deep red needles (a second crop was obtained by concentrating the solution; total yield 0·1 g.), m. p. >320° (Found: C, 59·5; H, 4·1; N, 10·7. $C_{13}H_{10}O_2N_2,HCl$ requires C, 59·4; H, 4·2; N, 10·7%). Light absorption in alcohol: $\lambda_{max.}$ 280, 308 mμ (log ε 4·16, 4·01); $\lambda_{min.}$ 255, 299, 340 mμ (log ε 3·89, 3·96, 3·46). On being kept, an alcoholic solution of the hydrochloride (0·1 g.) which had been diluted with distilled water (35 ml.) deposited the base as a *hydrate* in pale yellow needles, m. p. >320° (Found, in specimen dried in a vacuum at 80° for 1 hr.: C, 64·0; H, 4·8; N, 11·2. $C_{13}H_{10}O_2N_2,H_2O$ requires C, 63·9; H, 4·9; N, 11·5%). The *perchlorate* crystallised from alcohol in dark red needles, m. p. >320° (Found: C, 47·5; H, 3·4; N, 8·9. $C_{13}H_{10}O_2N_2,HClO_4$ requires C, 47·8; H, 3·4; N, 8·6%).

A mixture of the methene hydriodide (0·1 g.), acetic anhydride (5 ml.), and fused sodium acetate (0·2 g.) was heated under reflux for 15 min. and diluted with water (25 ml.). The yellow amorphous *acetyl* derivative, which eventually separated, was insoluble in ordinary solvents. Recrystallised from aqueous pyridine, this formed yellow needles containing solvent of crystallisation, m. p. *ca* 223—226° after sintering (Found, in a specimen dried in a vacuum at 70° for ½ hr.: C, 66·9; H, 4·8; N, 9·6. $C_{19}H_{16}O_5N_2,C_5H_5N$ requires C, 66·9; H, 4·9; N, 9·7%). Addition of water to a solution of the compound in acetic anhydride gave a solvent-free specimen which on repetition of the process had m. p. >320° [Found: C, 64·8; H, 4·6; N, 7·6; Ac, 35·6. $C_{13}H_7O_2N_2(CO{\cdot}CH_3)_3$ requires C, 64·8; H, 4·55; N, 8·0; Ac, 36·6%]. Light absorption in alcohol: $\lambda_{max.}$ 265 mμ (log ε 4·42); $\lambda_{min.}$ 250, 330 (log ε 4·33, 3·73); infl. at 289, 309 mμ (log ε 4·06, 4·01).

On being powdered in warm 2N-sodium hydrogen carbonate (30 ml.) the hydroiodide (0·18 g.) of the methene formed a clear yellow solution which on cooling deposited the yellow microcrystalline sodio-derivative (0·15 g.), soluble in hot aqueous sodium hydrogen carbonate and insoluble in ether. With warm water or acetic acid it gave the parent base.

Methylation of the C_{13} Base.—Methyl sulphate (0·52 ml.) was added gradually to a vigorously agitated solution of the aforementioned hydriodide (0·3 g.) in 2N-sodium hydroxide (30 ml.) containing sodium dithionite (0·3 g.), and the mixture subsequently acidified with acetic acid, giving the methylated methene, the *hydrochloride* of which separated from alcoholic hydrochloric acid in deep red needles (0·18 g.), m. p. >320° [Found: C, 60·6; H, 4·2; N, 10·2; OMe, 11·9. $C_{13}H_9ON_2(OMe),HCl$ requires C, 60·75; H, 4·7; N, 10·1; OMe, 11·2%]. The *perchlorate* formed deep red needles, m. p. >320°, from alcohol [Found: N, 8·5. $C_{13}H_9ON_2(OMe),HClO_4$ requires N, 8·2%]. Acetylation of the methylated methene gave the *diacetyl* derivative which

separated from alcohol in yellow needles, m. p. *ca* 300° (decomp.) (Found: OMe, 10·0. $C_{17}H_{13}O_3N_2$·OMe requires OMe, 9·6%).

5-Hydroxy-2-methylindole-3-aldehyde.—A solution of 5-hydroxy-2-methylindole (Beer, Clarke, Davenport, and Robertson, *J.*, 1951, 2029) (2 g.) in ether (30 ml.), containing hydrogen cyanide (10 ml.), at −5° was saturated with hydrogen chloride and kept at 0° overnight. A solution of the resulting colourless aldimine hydrochloride in water (40 ml.) was carefully neutralised with dilute aqueous ammonia, boiled for 5 min., and then allowed to cool, giving *5-hydroxy-2-methylindole-3-aldehyde* which separated from methanol in colourless needles (1·0 g.), m. p. 275° (decomp.) (Found: C, 68·5; H, 5·1. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in deep red needles, m. p. 291° (decomp.) (Found: C, 54·0; H, 3·8. $C_{16}H_{13}O_5N_5$ requires C, 54·1; H, 3·7%).

2-Ethoxycarbonyl-5-methoxyindole-3-aldehyde.—The Gattermann reaction with 2-ethoxycarbonyl-5-methoxyindole (3 g.) (Hughes and Lions, *J. Proc. Roy. Soc. N.S.W.*, 1937, **71**, 475) gave an aldimine hydrochloride which decomposed in hot water to *2-ethoxycarbonyl-5-methoxyindole-3-aldehyde*, forming pale yellow needles (1·7 g.), m. p. 240°, from alcohol (Found: C, 62·9; H, 5·2; N, 5·6. $C_{13}H_{13}O_4N$ requires C, 63·1; H, 5·3; N, 5·6%).

Indolylpyrrylmethenes from Pyrrole-2-aldehyde.—(*a*) When two drops of a saturated alcoholic solution of hydrogen chloride were added to 2-methylindole (0·11 g.) and pyrrole-2-aldehyde (0·1 g.) in the same solvent (3 ml.), a deep red colour developed rapidly and, upon addition of ether, red needles of the unstable methene hydrochloride separated. The absorption spectrum of the methene salt was measured as quickly as possible on the freshly prepared alcoholic solution: $\lambda_{max.}$ 272, 317 mμ; $\lambda_{min.}$ 240, 298 mμ.

(*b*) The condensation product of pyrrole-2-aldehyde and 5-hydroxy-2-methylindole in alcohol was also unstable. Light absorption (of the reaction mixture): $\lambda_{max.}$ 278, 318 mμ; $\lambda_{min.}$ 236, 297 mμ.

(*c*) On the addition of alcoholic hydrogen chloride to a solution of pyrrole-2-aldehyde and 3-methylindole, a red colour was produced but almost immediately was obscured by the separation of an amorphous dark brown solid.

2′-(4′-Ethoxycarbonyl-3′-hydroxy-5′-methylpyrryl)-3-(5-hydroxy-2-methylindolyl)methene (III).—(*a*) A solution of 5-hydroxy-2-methylindole-3-aldehyde (0·2 g.) and 3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole (Fischer and Loy, *Z. physiol. Chem.*, 1923, **128**, 75) (0·2 g.) in alcohol (50 ml.) containing saturated alcoholic hydrogen chloride (0·2 ml.) was concentrated until crystals appeared. The resulting *methene hydrochloride* crystallised from alcohol containing a trace of hydrogen chloride in bright red needles (0·28 g.), m. p. 232—234° (decomp.) (Found: C, 59·4; H, 5·35; N, 7·5. $C_{18}H_{18}O_4N_2$,HCl requires C, 59·5; H, 5·25; N, 7·7%). Light absorption in ethanol: $\lambda_{max.}$ 267, 301 mμ (log ε 4·10, 3·99); $\lambda_{min.}$ 245, 296 mμ (log ε 3·74, 3·89).

(*b*) The same compound, with identical properties and absorption spectrum, was obtained in rather low yield by the condensation of 5-hydroxy-2-methylindole and 4-ethoxycarbonyl-3-hydroxy-5-methylpyrrole-2-aldehyde (Fischer and Loy, *loc. cit.*) in a similar manner.

Prepared by the action of methyl sulphate (0·4 ml.) on a solution of the foregoing methene hydrochloride (0·3 g.) in 2N-sodium hydroxide (10 ml.) containing sodium dithionite (0·2 g.), the methyl ether of this methene was purified as its *perchlorate*, which formed red needles (0·21 g.), m. p. 228° [Found: C, 51·9; H, 4·7. $C_{18}H_{17}O_3N_2(OMe),HClO_4$ requires C, 51·75; H, 4·8%].

With hot acetic anhydride and sodium acetate the methene hydrochloride (0·2 g.) was converted into the *triacetyl* derivative, which separated from benzene in yellow rectangular prisms (0·15 g.), m. p. 210—212° [Found: C, 63·95; H, 5·3. $C_{18}H_{15}O_4N_2(CO{\cdot}CH_3)_3$ requires C, 63·7; H, 5·3%].

The following indolylpyrrylmethenes were prepared by the same general method.

2′-(4′-Ethoxycarbonyl-3′ : 5′-dimethyl-pyrryl)-3-(5-hydroxy-2-methylindolyl)methene (II), from 5-hydroxy-2-methylindole-3-aldehyde (0·2 g.) and 3-ethoxycarbonyl-2 : 4-dimethylpyrrole (0·2 g.), was obtained as the *hydrochloride* in bright red needles which could not be recrystallised; $\lambda_{max.}$ 246 mμ (log ε 3·94), $\lambda_{min.}$ 234, 300 mμ (log ε 3·87, 2·99) (Found: C, 63·0; H, 5·6. $C_{19}H_{20}O_3N_2$,HCl requires C, 63·2; H, 5·8%).

3′-(4′-Ethoxycarbonyl-2′-hydroxy-5′-methylpyrryl)-3-(2-ethoxycarbonyl-5-methoxyindolyl)methene (VI), from 2-ethoxycarbonyl-5-methoxyindole-3-aldehyde (0·2 g.) and 3-ethoxycarbonyl-5-hydroxy-2-methylpyrrole (0·17 g.), formed pale orange prisms (0·35 g.), m. p. 272—274°, from alcohol, $\lambda_{max.}$ 277, 302 mμ (log ε 4·06, 4·15), $\lambda_{min.}$ 260, 284, 340 mμ (log ε 3·98, 4·02, 3·84) (Found: C, 63·5; H, 5·4. $C_{21}H_{22}O_6N_2$ requires C, 63·3; H, 5·5%). This was also prepared with piperidine as the condensing agent.

2′-(4′-Ethoxycarbonyl-3′-hydroxy-5′-methylpyrryl)-3-(2-ethoxycarbonyl-5-methoxyindolyl)-methene (VII), from 2-ethoxycarbonyl-5-methoxyindole-3-aldehyde (0·2 g.) and 3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole (0·17 g.), separated from alcohol containing a little hydrochloric acid as the *hydrochloride* in orange needles (0·3 g.), m. p. 198—200° (decomp.), $\lambda_{max.}$ 299 mμ (log ε 4·27); $\lambda_{min.}$ 274 mμ (log ε 4·06) (Found: C, 57·8; H, 5·4. $C_{21}H_{22}O_6N_2$,HCl requires C, 58·0; H, 5·3%).

2′-(4′-Bromo-3′ : 5′-dimethylpyrryl)-3-(5-hydroxy-2-methylindolyl)methene (X), from 4-bromo-3 : 5-dimethylpyrrole-2-aldehyde (Fischer and Ernst, *Annalen*, 1928, **447**, 148) (0·2 g.) and 5-hydroxy-2-methylindole (0·15 g.), was obtained as the *hydrochloride* in orange needles (0·3 g.), m. p. 282° with darkening at 220°, which could not be recrystallised, $\lambda_{max.}$ 258, 289, 326 mμ (log ε 3·79, 3·97, 3·82), $\lambda_{min.}$ 244, 267, 302 (log ε 3·59, 3·63, 3·65) (Found: C, 52·2; H, 4·3. $C_{16}H_{15}ON_2Br$,HCl requires C, 52·2; H, 4·4%).

3′-(5′-Bromo-2′ : 4′-dimethylpyrryl)-3-(5-hydroxy-2-methylindolyl)methene (XI), from 5-bromo-2 : 4-dimethylpyrrole-3-aldehyde (Fischer and Zeile, *Annalen*, 1928, **462**, 221) (0·4 g.) and 5-hydroxy-2-methylindole (0·3 g.), was obtained as the *hydrochloride*, in deep red prisms (0·15 g.), m. p. 171°, $\lambda_{max.}$ 275, 313 mμ (log ε 4·14, 3·86), $\lambda_{min.}$ 252, 300, 340 (log ε 3·91, 3·79, 3·49) (Found: C, 52·1; H, 4·2; N, 7·4. $C_{16}H_{15}ON_2Br$,HCl requires C, 52·2; H, 4·4; N, 7·6%).

Di-3-(5-hydroxy-2-methylindolyl)methene (IV).—(*a*) In alcoholic hydrogen chloride at room temperature a mixture of 5-hydroxy-2-methylindole (0·2 g.) and 5-hydroxy-2-methylindole-3-aldehyde (0·2 g.) gave *di-3-(5-hydroxy-2-methylindolyl)methene hydrochloride* which formed red needles (0·38 g.) (from alcohol), m. p. 320° (Found: C, 66·3; H, 5·1; N, 8·3. $C_{19}H_{16}O_2N_2$,HCl requires C, 66·5; H, 5·0; N, 8·2%). Light absorption in alcohol: $\lambda_{max.}$ 283 mμ (log ε 4·36); $\lambda_{min.}$ 244 mμ (log ε 3·61).

(*b*) The same product was obtained by heating a solution of the indole-aldehyde in 5% alcoholic hydrogen chloride for 30 min., and by the action of hydrogen chloride on a solution of 5-hydroxy-2-methylindole and formic acid in ether.

(*c*) The di-indolylmethene was the only product isolated from condensations carried out under the standard conditions (*i.e.*, with alcoholic hydrogen chloride) between 5-hydroxy-2-methylindole-3-aldehyde and 3-ethoxycarbonyl-5-hydroxy-2-methylpyrrole (Fischer and Müller, *Z. physiol. Chem.*, 1923, **132**, 75), 5-acetoxy-3-ethoxycarbonyl-2-methylpyrrole, 4-ethoxycarbonyl-2-hydroxypyrrole (Grob and Ankli, *Helv. Chim. Acta*, 1949, **32**, 2021), 2-acetoxy-3-acetyl-4-ethoxycarbonylpyrrole, 3-acetoxy-4-ethoxycarbonyl-2-hydroxypyrrole (Grob and Ankli, *loc. cit.*), and 2-hydroxypyrrole (Langenbeck and Boser, *Ber.*, 1951, **84**, 526). The condensation of 5-hydroxy-2-methylindole with 4-ethoxycarbonyl-2-hydroxy-5-methylpyrrole-3-aldehyde (Fischer and Müller, *loc. cit.*) also led to the di-indolylmethene.

2′-(3′-Ethoxycarbonyl-5′-hydroxy-4′-methylpyrryl)-3-(5-hydroxy-2-methylindolyl)methene (IX).—On being heated under reflux for 4 hr. a solution of 5-hydroxy-2-methylindole (0·3 g.) and 2-bromomethyl-3-ethoxycarbonyl-5-hydroxy-4-methylpyrrole (Fischer and Adler, *Z. physiol. Chem.*, 1931, **197**, 269) (0·3 g.) in methanol (4 ml.) became bright red and on cooling slowly deposited the *methene*. Recrystallised from methanol, this product formed red plates (0·15 g.), m. p. 189° with darkening from 120°, $\lambda_{max.}$ 286 mμ (log ε 4·14), $\lambda_{min.}$ 258 mμ (log ε 4·06) (Found: C, 66·0; H, 5·7; N, 8·5. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5; N, 8·6%).

p-Dimethylaminophenyl-2′-(4′-ethoxycarbonyl-3′-hydroxy-5′-methylpyrryl)methene hydrochloride (XIV), from *p*-dimethylaminobenzaldehyde and 3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole, separated from alcoholic hydrogen chloride in violet needles, m. p. 162—164° (Found: N, 8·0. $C_{17}H_{20}O_3N_2$,HCl requires N, 8·3%).

With 3-ethoxycarbonyl-5-hydroxy-2-methylpyrrole (0·5 g.) *p*-dimethylaminobenzaldehyde (0·44 g.) gave the *hydrochloride* of *p*-dimethylaminophenyl-3′-(4′-ethoxycarbonyl-2′-hydroxy-5′-methylpyrryl)methene (XVI), forming orange prisms (0·8 g.), m. p. 207—209°, from alcohol containing a little hydrochloric acid (Found: N, 8·0; Cl, 11·2. $C_{17}H_{20}O_3N_2$,HCl requires N, 8·3; Cl, 10·9%).

Similarly *p*-hydroxybenzaldehyde (0·7 g.) and 3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole (0·9 g.) gave *2′-(4′-ethoxycarbonyl-3′-hydroxy-5′-methylpyrryl)-p-hydroxyphenylmethene* (XIX; R = H) in clusters of bright yellow needles (1·3 g.), m. p. 278° (decomp.) (Found: C, 66·2; H, 5·7; N, 5·4. $C_{15}H_{15}O_4N$ requires C, 66·0; H, 5·5; N, 5·1%). Prepared with boiling acetic anhydride and sodium acetate, the *diacetyl* derivative separated from 95% alcohol in yellow rectangular plates, m. p. 212—214° (Found: N, 3·8. $C_{19}H_{19}O_6N$ requires N, 3·9%). With methyl sulphate and aqueous sodium hydroxide the methene (XIX) gave *2′-(4′-ethoxycarbonyl-3′-hydroxy-5′-methylpyrryl)-p-methoxyphenylmethene* (XIX; R = Me), forming yellow plates, m. p. 220°, from alcohol identical with a specimen (0·58 g.) prepared by the condensation of

3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole (0·4 g.) and *p*-anisaldehyde (0·4 g.) in alcohol (24 ml.) and concentrated hydrochloric acid (2 drops) (Found: C, 66·3; H, 5·7; N, 4·8. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9; N, 4·9%).

3′-(4′-*Ethoxycarbonyl*-2′-*hydroxy*-5′-*methylpyrryl*)-p-*hydroxyphenylmethene* (XX; R = H), from *p*-hydroxybenzaldehyde (0·7 g.) and 3-ethoxycarbonyl-5-hydroxy-2-methylpyrrole (0·9 g.), separated from alcohol in yellow needles (1·4 g.), m. p. 224—226° (Found: N, 5·1. $C_{15}H_{15}O_4N$ requires N, 5·1%). The *methyl ether* (XX; R = Me) formed bright yellow cubes, m. p. 194°, from alcohol (Found: C, 66·7; H, 5·9; N, 4·8. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9; N, 4·9%). This was identical with the methene obtained when *p*-hydroxybenzaldehyde was replaced by anisaldehyde in the foregoing condensation.

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Interaction of Polynitro-compounds with Aromatic Hydrocarbons and Bases. Part XII. Complexes of* N-*Alkylated Anilines with* s-*Trinitrobenzene and* s-*Trinitrotoluene.*

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[Reprint Order No. 5264.]

Colour measurements have been used to derive association constants for the interactions of *N*-alkylanilines with *s*-trinitrobenzene and *s*-trinitrotoluene in *cyclo*hexane. The amounts of interaction between a nitro-compound and members of homologous series have been compared for the *N*-mono- and the *NN*-di-*n*-alkylaniline series. For the higher members of both series, increased chain-length results in complexes of greater stability. The wave-length of maximum absorption due to the interaction rises with the first few members of both these series, thereafter remaining sensibly constant. The effect of changing the solvent has also been measured.

The results are discussed mainly in the light of Mulliken's concept of charge-transfer complexes (*J. Amer. Chem. Soc.*, 1952, **74**, 811; *J. Phys. Chem.*, 1952, **56**, 801).

INTERACTIONS between nitro-compounds (Lewis acids) and bases, including Lewis bases such as aromatic hydrocarbons, appear to be of two kinds. There are those which take place slowly, usually with change of colour, and yield new compounds which can be isolated and to which definite structures can be assigned. Such is the compound obtained by Meisenheimer (*Annalen*, 1902, **323**, 219) from the action of the bases OMe^- and OEt^- on *s*-trinitrophenetole and *s*-trinitroanisole respectively. These interactions involve *s*-orbital functions of the carbon atoms and result in the formation of new covalent bonds. Secondly, there are interactions which take place instantaneously and may or may not involve an alteration in the electronic absorption bands. No new localised bonds are apparently formed, the forces involved being those of dispersion, polarisation, multi-pole and hydrogen bonding.

An important interaction within this second class is the charge-transfer type of complex described by Mulliken (*J. Amer. Chem. Soc.*, 1952, **74**, 811; *J. Phys. Chem.*, 1952, **56**, 801). The components of the complexes are presumably held together by the forces arising from the resonance of a no-bond structure involving dispersion, polarisation, and multi-pole forces, with a structure in which there is donation of an electron from one molecule to another (the dative function). It is expected that this type of interaction will permit an excited state not corresponding to higher electronic levels in either component separately, but characteristic of the complex as a whole. Transitions to this state should give rise to absorption in the visible or near ultra-violet region of the spectrum. There is evidence (Ross, Bassin, Finkelstein, and Leach, *J. Amer. Chem. Soc.*, 1954, **76**, 69; Ross and Kuntz, *ibid.*, p. 74) for two types of interaction between two species of molecules, one involving only dispersion and similar forces, the other being a charge-transfer interaction. Optical

* Part XI, *J.*, 1953, 3817.

methods will normally give an estimate of the degree of charge-transfer complex formation, whereas some other methods such as partition will give a measure of the sum of all types of interaction.

In the present communication we record a study of the interaction of *N*-alkylanilines with *s*-trinitrobenzene and *s*-trinitrotoluene in solution. Light absorption assumed to be characteristic of this type of interaction has been used in an application of the colorimetric method described by Foster, Hammick, and Wardley (*J.*, 1953, 3817) to determine the degree of association.

In the case of interactions of *N*-alkylanilines with *s*-trinitrobenzene and *s*-trinitrotoluene the colours produced correspond to absorption away from the absorption bands of either component so that the methods involving successive approximations are avoided. Most of the determinations were made in *cyclo*hexane. This solvent was chosen primarily because of the small interaction to be expected between solvent and solutes. It also has very low extinction coefficients in the region 200—600 mμ and, compared with many other paraffins, is relatively easy to purify.

An association constant K is defined as:

$$K = [AB]/[A][B] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where [AB], [A], and [B] are the equilibrium concentrations in mole/l. of the complex and the two components respectively. If a and b are the concentrations of the two components on the assumption that there is no interaction, and $b \gg a$, it has been shown (Foster, Hammick, and Wardley, *loc. cit.*) that then:

$$Ka\varepsilon - KD = D/b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where ε is the extinction coefficient of the complex, and D the optical density of the solution assumed to be wholly due to the complex. K and ε may be evaluated by plotting D/b against D for a series of solutions of varying b and constant a.

By this method we have determined K and ε for a series of *N*-alkylaniline–*s*-trinitrobenzene and –*s*-trinitrotoluene interactions in various solvents.

Experimental

All solutions were made up by weight in standardised glassware. The optical densities were measured by a Beckman Quartz Spectrophotometer (model DU), 10 mm. cells being used throughout.

Materials.—The *N*-alkylanilines were purified by standard methods. The monoalkylanilines were purified as their hydrochlorides except *N*-*n*-pentylaniline which was purified as its toluene-*p*-sulphonyl derivative. The dialkylanilines were purified by fractionation under reduced pressure. In particular the following hitherto unprepared alkylanilines were obtained by heating the respective alkyl bromides with aniline under the conditions given in Table 1.

Table 1. *Preparation of new alkylanilines.*

No.	Product, *N*-subst.	Alkyl bromide (moles)	Aniline (moles)	KOH (moles)	Temp.	Time (hr.)	Yield (%)
1	*N*-*n*-Nonyl	0·12	0·54	—	100°	12	55
2	*N*-*n*-Decyl	0·5	2·7	—	100	10	46
3	*N*-*n*-Undecyl	0·1	0·5	—	100	10	40
4	*NN*-Di-*n*-octyl	0·2	0·1	0·2	130	12	42
5	*NN*-Di-*n*-decyl	0·12	0·06	0·12	130	12	45

	Found (%)					Required (%)			
	C	H	N	Cl	Formula	C	H	N	Cl
1	82·3	11·6	6·0	—	$C_{15}H_{25}N$	82·2	11·4	6·4	—
1, HCl	70·4	10·3	5·5	13·9	$C_{15}H_{25}N,HCl$	70·5	10·2	5·5	13·9
2	82·4	11·6	6·0	—	$C_{16}H_{27}N$	82·4	11·6	6·0	—
2, HCl	71·7	10·4	5·2	—	$C_{16}H_{27}N,HCl$	71·2	10·5	5·2	—
3	83·0	11·7	—	—	$C_{17}H_{29}N$	82·6	11·7	—	—
3, HCl	72·0	10·6	4·9	12·7	$C_{17}H_{29}N,HCl$	71·9	10·7	4·9	12·5
4	82·9	12·5	4·5	—	$C_{22}H_{39}N$	83·3	12·3	4·4	—
4, HCl	—	—	—	9·7	$C_{22}H_{39}N,HCl$	—	—	—	10·0
5	83·5	12·4	3·6	—	$C_{26}H_{47}N$	83·6	12·6	3·7	—
5, HCl	—	—	—	8·5	$C_{26}H_{47}N,HCl$	—	—	—	8·6

Aniline was prepared by the hydrolysis of carefully purified acetanilide.

The b. p.s and refractive indices of the alkylanilines and the m. p.s of some of their hydrochlorides are given in Table 2.

TABLE 2. *Mono- and di-alkylanilines.*

N-Substituent	B. p./mm.	n_D^{20}	M. p. of hydrochloride	*N*-Substituent	B. p./mm.	n_D^{20}
H	76°/15	1·5863	198°	Di-*n*-propyl	126°/10	1·5272
Methyl	92°/20	1·5704	121	Di-*n*-butyl	96°/2	1·5188
Ethyl	97—97·5°/20	1·5559	176	Di-*n*-pentyl	164°/15	1·5130
n-Propyl ...	100°/10	1·5412	150	Di-*n*-hexyl	188—189°/30	1·5080
n-Butyl	124°/20	1·5331	115	Di-*n*-octyl	197—198°/3 [b]	1·5007
n-Pentyl ...	125°/15	1·5275	93	Di-*n*-decyl	210°/0·7 [c]	1·4966
n-Hexyl	144°/12	1·5230	75—76			
n-Heptyl ...	160°/20 [a]	1·5189	78			
n-Octyl	200°/36	1·5150	82			
n-Nonyl	178°/9	1·5120	84			
n-Decyl	198°/11	1·5094	88			
n-Undecyl ...	205°/10	1·5083	89			
n-Dodecyl ...	M. p. 28°	solid	93			
Dimethyl ...	72—72·5°/10	1·5585	—			
Diethyl	91°/10	1·5421	—			
*iso*Propyl ...	107°/8	1·5392	175·5			
tert.-Butyl ...	92—93°/20	1·5374	—			
*cyclo*Pentyl	144°/19	1·5650	157·5			
*cyclo*Hexyl	167°/24	1·5602	203			
*cyclo*Heptyl	170°/15	1·5605	—			

[a] This agrees with the value given by Hickinbottom (*J.*, 1937, 1119), 160—161°/21 mm., but not with that, 125°/30 mm., quoted by Emerson (*J. Amer. Chem. Soc.*, 1938, **60**, 2023). [b] Hydrochloride, m. p. 99° (not sharp). [c] Hydrochloride, m. p. 101° (not sharp).

*cyclo*Hexane was mechanically stirred with 20% oleum for 12 hr., then washed with dilute potassium permanganate solution and with water, and dried ($CaCl_2$) : it had b. p. 81°/762 mm., n_D^{20} 1·4267.

n-Hexane was washed six times with 10% oleum, then with water, and dried ($CaCl_2$); the main fraction had b. p. 68·5—69·5°/761 mm., n_D^{20} 1·3758.

n-Heptane : A pure sample, washed once with 10% oleum and fractionated, had b. p. 98°/758 mm., n_D^{20} 1·3877.

Chloroform, washed six times with water, dried ($CaCl_2$), and distilled, had b. p. 61°/758 mm., n_D^{20} 1·4450.

Carbon tetrachloride, purified as described by Smitz-Dumont (*Chem. Ztg.*, 1897, **21**, 511), had b. p. 77°/763 mm., n_D^{20} 1·4600.

s-Tetrachloroethane, distilled from potassium carbonate, had b. p. 146°/761 mm., n_D^{20} 1·4950.

1 : 4-Dioxan, purified as recommended by Vogel ("A Textbook of Practical Organic Chemistry," Longmans, London, 1948, p. 175), had m. p. 11·0°, n_D^{20} 1·4220.

Decalin (*cis-trans* mixture), purified as prescribed by Zelinsky and Turowa-Pollack (*Ber.*, 1932, **65**, 1299), had b. p. 192°/763 mm., n_D^{20} 1·4792.

s-Trinitrobenzene, recrystallised four times from alcohol, had m. p. 122°.

s-Trinitrotoluene, recrystallised four times from alcohol, had m. p. 80·5°.

NNN'N'-Tetramethyl-*p*-phenylenediamine was purified as the hydrochloride, the free base being subsequently distilled *in vacuo*. It had m. p. 51°.

TABLE 3. ($a = 3·76 \times 10^{-4}$M.)

No.	Wavelength : b(M)	450 mμ D	450 mμ D/b	460 mμ D	460 mμ D/b	470 mμ D	470 mμ D/b	480 mμ D	480 mμ D/b	490 mμ D	490 mμ D/b	500 mμ D	500 mμ D/b
1	0·270	0·339	1·25	0·345	1·28	0·351	1·30	0·352	1·30	0·319	1·18	0·296	1·10
2	0·240	0·325	1·35	0·330	1·37	0·338	1·40	0·338	1·40	0·310	1·29	0·285	1·19
3	0·210	0·315	1·50	0·320	1·52	0·325	1·55	0·321	1·53	0·295	1·40	0·273	1·30
4	0·179	0·295	1·65	0·301	1·68	0·307	1·72	0·305	1·70	0·279	1·56	0·260	1·45
5	0·148	0·273	1·84	0·280	1·89	0·286	1·93	0·286	1·93	0·257	1·73	0·242	1·63
6	0·118	0·248	2·10	0·252	2·14	0·256	2·17	0·257	2·18	0·231	1·96	0·217	1·84
7	0·0875	0·212	2·42	0·217	2·48	0·222	2·54	0·222	2·54	0·200	2·29	0·187	2·14

The following are details of a typical determination of an association constant in the case of *NN*-dimethylaniline–*s*-trinitrobenzene in *cyclo*hexane solution; the results given in Tables 4—7 were obtained by the same procedure.

Association Constant for the Interaction between NN-*Dimethylaniline and* s-*Trinitrobenzene in* cyclo*Hexane Solution.*—Beer's law was shown to be obeyed by *NN*-dimethylaniline solutions in

TABLE 4. *Complexes with* s-*trinitrobenzene in* cyclo*hexane solution.*

N-Substituent in aniline	*K* (l./mole)	λ (mμ)	ε_λ (l. mole^{-1} cm.$^{-1}$)	Temp.	*N*-Substituent in aniline	*K* (l./mole)	λ (mμ)	ε_λ (l. mole^{-1} cm.$^{-1}$)	Temp.
H	3·0	390	1700	20·0°	Diethyl	6·5	501	1120	20·0°
	3·3	430 [1]	—	20·0		6·6	501	1050	19·5
Methyl	7·7	435	1180	20·0	Di-*n*-propyl	6·5	504	1150	20·0
	7·8	435	1190	18·0		6·4	504	—	20·0
Ethyl	8·4	445	1150	19·8	Di-*n*-butyl	7·4	505	1120	18·0
	8·4	445	1100	19·0		7·4	505	1100	18·0
n-Propyl	7·3	445	1230	18·5	Di-*n*-pentyl	9·0	510	990	19·0
	7·2	445	1190	18·5		9·0	510	1000	19·0
n-Butyl	8·2	445	1180	19·0	Di-*n*-hexyl	9·8	510	980	19·0
	8·6	445	1220	24·5		9·6	510	980	18·7
	8·2	445	1200	19·0	Di-*n*-octyl	10·0	510	980	18·5
	8·2	445	1190	19·0		10·0	510	970	19·0
n-Pentyl	8·0	445	1120	20·0	Di-*n*-decyl-aniline	9·9	511	960	18·4
	8·0	445	1180	19·0		10·2	511	960	20·0
n-Hexyl	9·1	445	1160	20·0	*iso*Propyl-aniline	6·7	445	1180	20·0
	8·8	445	1200	19·0		6·7	445	1240	19·5
n-Heptyl	9·8	445	1140	18·3	*tert.*-Butyl-aniline	5·5	440 [1]	620	20·0
	9·4	445	1180	18·3					
n-Octyl	9·0	445	1220	20·0	*cyclo*Pentyl-aniline	8·5	450	1180	20·0
	9·2	445	1260	18·0					
n-Nonyl	10·7	445	1190	18·0	*cyclo*Hexyl-aniline	9·3	448 [1]	1150	18·0
	10·5	445	1250	18·0		9·0	450	1060	20·0
n-Decyl	11·3	445	1190	18·0	*cyclo*Heptyl-aniline	9·2	450	1140	18·5
	11·1	470 [1]	1120	18·0		9·2	445 [1]	1200	19·0
	11·2	445	1140	20·0	Tetramethyl-*p*-phenylene-diamine	20·4	600	—	19·0
n-Undecyl	11·3	445	1080	18·0					
	11·1	445	1160	18·0					
n-Dodecyl	11·6	445	1070	18·0					
	11·6	445	—	18·0					
Dimethyl	9·3	450 [1]	1260	20·0					
	9·5	460 [1]	1280	20·0					
	9·5	470 [1]	1300	20·0					
	9·5	480 [1]	1300	20·0					
	9·5	490 [1]	1180	20·0					
	9·6	475	1300	20·0					

[1] Wave-lengths other than $\lambda_{max.}$.

TABLE 5. *Complexes with* s-*trinitrotoluene in* cyclo*hexane solution.*

N-Substituents in aniline	*K* (l./mole)	λ (mμ)	Temp.	*N*-Substituents in aniline	*K* (l./mole)	λ (mμ)	Temp.
Methyl	3·1	420 [a]	21·0°	Di-*n*-butyl	2·5	464	18·0°
Ethyl	3·8	420	20·0	Di-*n*-pentyl	3·0	465 [b]	18·5
Dimethyl	5·8	430	19·0	Di-*n*-hexyl	3·5	467 [c]	18·0
Diethyl	2·4	440	20·0	*iso*Propyl	2·7	440 [a]	20·0
Di-*n*-propyl	2·3	464	20·0	*tert.*-Butyl	2·2	440 [a]	20·0

[a] Wave-lengths other than $\lambda_{max.}$. [b] $\varepsilon_{max.}$ = 640 l. mole^{-1} cm.$^{-1}$. [c] $\varepsilon_{max.}$ = 600 l. mole cm.$^{-1}$.

TABLE 6. *The complex* NN-*dimethylaniline–*s-*trinitrobenzene in solvents other than* cyclo*hexane.*

Solvent	*K* (l./mole)	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$ (l. mole^{-1} cm.$^{-1}$)	Temp.
n-Hexane	8·2	465	1120	19·0°
n-Heptane	8·2	466	1180	19·4
Decalin	7·2	472	1300	19·4
Carbon tetrachloride	3·4	484	1340	19·0
Chloroform	1·3	486	1140	21·0
s-Tetrachloroethane	0·2	492	—	20·0
1 : 4-Dioxan	0·15	469	—	18·5

TABLE 7. *Complexes with* s-*trinitrobenzene in* n-*heptane.*

Base	*K* (l./mole)	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$ (l. mole^{-1} cm.$^{-1}$)	Temp.
N-*n*-Butylaniline	6·2	450	1200	25·0°
N-*n*-Decylaniline	7·2	450	1180	25·0

*cyclo*hexane. Owing to the low solubility, Beer's law for *s*-trinitrobenzene in *cyclo*hexane could not be verified. However the law has been shown to hold for chloroform solutions of *s*-trinitrobenzene.

A series of solutions were made up by weight containing a constant amount of *s*-trinitrobenzene (A), namely, $3{\cdot}76 \times 10^{-4}$M, the concentration of *NN*-dimethylaniline (B) varying as indicated in Table 3. The absorption spectra of solution (1) and a solution of *NN*-dimethylaniline alone in *cyclo*hexane at the same concentration as in (1) were measured in the wave-length region 330—550 mμ to determine the position of the charge-transfer spectrum (Fig. 1). The optical densities of solutions 1—7 were measured at wave-length intervals of 10 mμ from 450 to 500 mμ. The resulting optical densities together with the respective D/b ratios are given in Table 3 from which the respective K and C values in Table 4 are obtained.

The mean temperature of the cell compartment is recorded for each determination in

FIG. 1.

A, Spectrum of NN-*dimethylaniline* (0·27M) *in* cyclo*hexane.*
B, Spectrum of a mixture of NN-*dimethylaniline* (0·27M) *and* s-*trinitrobenzene* ($3{\cdot}76 \times 10^{-4}$M).

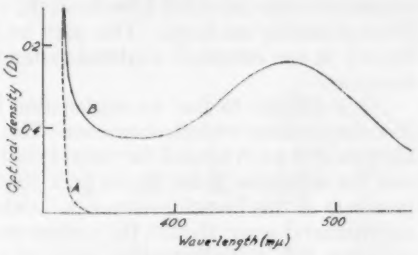


FIG. 2. *Association constant* (*K*) v. *alkyl chain-length of* N-*mono*-n-*alkylaniline*–s-*trinitrobenzene complexes in* cyclo*hexane.*

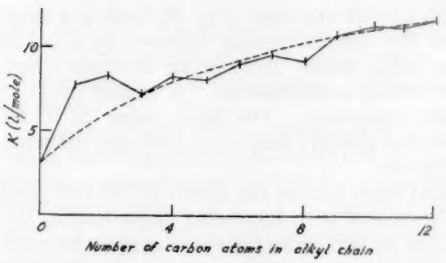
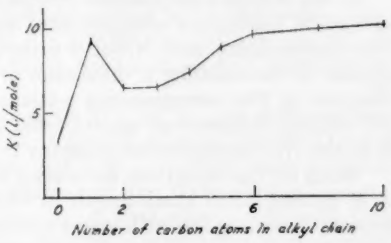


FIG. 3. *Association constant* (*K*) v. *alkyl chain-length of* NN-*di*-n-*alkylaniline*–s-*trinitro-benzene complexes in* cyclo*hexane.*



Tables 4—7. In the small range of temperatures involved, the effect of any temperature coefficient appears to be small.

In the *N*-mono- and *NN*-di-*n*-alkylaniline series of complexes with *s*-trinitrobenzene, the determinations have all been repeated at least once in the temperature range 18—20°, with samples of alkylaniline prepared by at least two separate syntheses from different samples of the alcohol, with the exception of *N*-*n*-nonyl- and *N*-*n*-undecyl-aniline. Agreement in the final values of K are within ±2·1% of the mean values, with the exception of aniline for which two values within ±5% were obtained. The limits of the differences of the experimental values of K are in every case ±0·2 l./mole. These limits are represented by vertical lines in Figs. 2 and 3. In the case of *NN*-dimethylaniline–*s*-trinitrobenzene in *cyclo*hexane it has been shown that the association constant derived from optical-density measurements over a wave-length range of 50 mμ is constant within this experimental error of 0·2 l./mole.

DISCUSSION

In this discussion it is assumed, in agreement with McConnell and Landauer (*J. Amer. Chem. Soc.*, 1952, **74**, 1221), and Mulliken (*J. Phys. Chem.*, 1952, **56**, 801), that the alkylaniline–*s*-trinitrobenzene and –*s*-trinitrotoluene complexes studied are charge-transfer complexes. At the concentrations and wave-lengths used no evidence for interactions

involving a ratio of component molecules other than 1 : 1 has been found. McConnell and Landauer (*loc. cit.*) suggest the presence of 2 : 1 as well as 1 : 1 complexes in an investigation of the interaction of aniline with *s*-trinitrobenzene in chloroform solution. However, these solutions were several times more concentrated than any used in the present work.

Complexes in cyclo*Hexane.*—The association constants (K) for the *N*-alkylaniline–*s*-trinitrobenzene complexes range from 3·0 to 11·6 l./mole, and from 2·2 to 5·8 l./mole for the *s*-trinitrotoluene complexes. These results indicate that *s*-trinitrotoluene is a weaker Lewis acid than *s*-trinitrobenzene.

In the monoalkylaniline series, the values of K for the respective complexes with *s*-trinitrobenzene tend to increase with increasing alkyl chain-length (Fig. 2), the largest increment in K being from aniline to *N*-methylaniline. If a smooth curve is drawn as a correlation of K with alkyl chain-length, there appear to be deviations greater than the estimated error of $\pm$0·2 l./mole in K. In particular, values of K for *N*-methyl- and *N*-ethyl-aniline are large. This may be due to hyperconjugation increasing the electron density in the extended π-orbital system of the alkylanilines, thus increasing their Lewis basicities.

It is difficult to find an explanation for the low value of the association constant of *N*-*n*-octylaniline–*s*-trinitrobenzene. This aniline was synthesised twice from different samples of *n*-octyl alcohol for each of the two determinations of K. The infra-red spectrum and the refractive index of the pure base appear to be normal by comparison with other members of this homologous series. Other deviations in Fig. 2 are close to the estimated experimental error, though the comparative smoothness in the variation of K in the corresponding *NN*-di-*n*-alkylaniline series of complexes suggests that these deviations may be real. Lack of smoothness might be expected as doubtless many factors, some implicitly steric, are involved in complex formation. Packing effects of the alkyl chain may account for some of the deviations (Anderson and Hammick, *J.*, 1950, 1089).

In the *NN*-di-*n*-alkylaniline complexes with *s*-trinitrobenzene (Fig. 3) there is a large increase in association constant from aniline to *NN*-dimethylaniline, followed by a fall to *NN*-diethylaniline and *NN*-di-*n*-propylaniline, after which there is an increase which appears to be reaching a maximum at about *NN*-di-*n*-decylaniline. A similar effect is observed in the corresponding *s*-trinitrotoluene complexes. The large value of K for *NN*-dimethylaniline may again be due to hyperconjugation; this effect may also influence K in the *NN*-diethylaniline complex to some extent.

When all the deviations have been considered there remain the trends in the two plots of K against alkyl chain-length in which K increases with increasing chain-length, the increase becoming less with longer chains. In the dialkyl series the curve appears to reach a maximum at a chain-length of about ten carbon atoms; in the monoalkyl series K is still increasing when there are twelve atoms in the alkyl chain. No increase would be expected after *n*-propyl or *n*-butyl, and with longer chains a slight diminution might be expected owing to steric interference. Thus Jones (*J.*, 1935, 1831), when he compared the rates of chlorination of ethers *p*-X·C_6H_4·OR (X = Cl, Br, CO_2H), found that the effect of the group OR increased in the series R = Me, Et, Pr^n, becoming constant at Bu^n, thereafter falling slightly to R = octadecyl. In contrast to this, Robinson and Smith (*J.*, 1931, 251) have shown that in the nitration of ethers *p*-MeO·C_6H_4·OR the effect of R = octadecyl is greater than of R = Bu^n or Pr^n. These results of Robinson and Smith correspond with those obtained in the present work, and it seems unlikely that they can be explained by a simple inductive effect. In the case of the polynitrobenzene–alkylaniline complexes however, a dipole induced-dipole structure may be of significance in the no-bond structure in the ground state. The polarisability of the alkylanilines increases with increasing chain-length, and it may be a combination of this increased polarisability with the inductive effect of the alkyl groups in these alkylanilines which results in the observed general relationship between K and alkyl chain-length.

In the series of complexes of *s*-trinitrobenzene and *s*-trinitrotoluene with *N*-methyl-, *N*-ethyl-, *N-iso*propyl-, and *N-tert.*-butyl-aniline the association constants in *cyclo*hexane increase from *N*-methyl- to *N*-ethyl-aniline, thereafter decreasing. Alternative explanations, *e.g.*, loss of hyperconjugation (Cardwell and Kilner, *J.*, 1951, 2435) or steric

hindrance, might account for the decrease in the respective association constants after *N*-ethylaniline.

There appears to be little correlation between pK_a values of the alkylanilines and their respective association constants with s-trinitrobenzene (Table 8). This is hardly surprising as the pK_a value is a measure of the Brønsted basicity, while the association constant is presumably a measure of the Lewis basicity of the alkylanilines.

The wave-lengths of maximum absorption of the complexes ($\lambda_{max.}$) have been determined from plots of the spectra of the mixtures. As the components in general do not absorb appreciably in the region of absorption by the complex, it is possible by drawing tie-lines over the upper portion of the absorption curve to obtain an estimate of $\lambda_{max.}$. It is, of course, recognised that this value is only an approximate estimation. $\lambda_{max.}$ increases from 390 to 430 mμ in going from aniline–*s*-trinitrobenzene to *N*-methylaniline–*s*-trinitrobenzene, followed by the smaller increase to 445 mμ for the *N*-ethylaniline complex. There-

TABLE 8.

Base	K [1] (l./mole)	pK_a (H_2O; 25°)	pK_a (75% alcohol)	Base	K [1] (l./mole)	pK_a (H_2O; 25°)	pK_a (75% alcohol)
Aniline	3·1	4·60 [2]	4·14 [2]	*NN*-Dimethylaniline ...	9·5	5·12 [2]	3·90 [2]
N-Methylaniline	7·7	4·85 [3]	—	*NN*-Diethylaniline	6·5	6·56 [3]	5·41 [2]
N-Ethylaniline	8·4	5·11 [3]	4·25 [2]	*NN*-Di-*n*-propylaniline	6·4	5·59 [3]	—
N-*n*-Propylaniline ...	7·2	5·02 [3]	—	*NN*-Di-*n*-butylaniline...	7·4	—	4·51 [2]
N-*n*-Butylaniline ...	8·2	—	4·02 [2]	*NN*-Di-*n*-hexylaniline...	9·7	—	4·39 [2]
N-*n*-Hexylaniline ...	8·9	—	4·02 [2]	*NN*-Di-*n*-octylaniline ...	10·0	—	4·37 [2]
N-*n*-Octylaniline ...	9·1	—	4·02 [2]				

[1] Association constant of the interaction with *s*-trinitrobenzene in *cyclo*hexane. [2] Wepster, personal communication. [3] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.

after up to the *N*-*n*-dodecylaniline complex, $\lambda_{max.}$ remains constant in the monoalkyl series of aniline complexes with *s*-trinitrobenzene. There is a similar regularity in the *NN*-dialkylaniline series of complexes. With *s*-trinitrotoluene the corresponding wave-lengths are shorter.

Compared with the correlation of K with chain-length, that of $\lambda_{max.}$ is comparatively simple and may possibly be related to the fact that the inductive effect of the alkyl groups becomes constant after the first few members. Assuming that the excited state is mainly the dative structure A^-B^+ (A representing the nitro-compound, and B the alkylaniline) and that $\lambda_{max.}$ is a function of the energy of excitation from the ground state to this level, then it is clear that the inductive effect of the alkyl groups will have a large effect on this dative structure compared with the effect on the no-bond structure which largely determines the ground state. $\lambda_{max.}$ may therefore be expected to become constant as the inductive effect of the alkyl group becomes constant. On the other hand, K takes account of a ground-state no-bond structure in which the dative structure participates only to a small extent (Mulliken, *loc. cit.*).

The values of molar extinction coefficient at the wave-length of maximum absorption ($\varepsilon_{max.}$) for the *N*-monoalkylaniline–*s*-trinitrobenzene complexes are all within the range 1010—1260 l. mole^{-1} cm.$^{-1}$. $\varepsilon_{max.}$ for aniline is considerably higher (1700 l. mole^{-1} cm.$^{-1}$). For the *NN*-dialkylaniline–*s*-trinitrobenzene complexes $\varepsilon_{max.}$ gradually falls from 1270 to 960 l. mole^{-1} cm.$^{-1}$. *N-tert.*-Butylaniline–*s*-trinitrobenzene is exceptional in exhibiting no maximum in the wave-length range 360—800 mμ; also $\varepsilon_{445\ m\mu}$ is low (660 l. mole^{-1} cm.$^{-1}$) compared with the extinction coefficient of the corresponding *N*-*n*-butylaniline complex. The two values of $\varepsilon_{max.}$ determined for *s*-trinitrotoluene complexes are considerably lower than the values of the corresponding *s*-trinitrobenzene complexes.

The observation that the intensities of the charge-transfer transitions of the interactions of *N*-alkylanilines with *s*-trinitrobenzene show no strong correlation with the association constants of the interactions or with the wave-lengths of the transitions agrees with the conclusions made after a study of the interaction of iodine with various Lewis bases by McConnell, Ham, and Platt (*J. Chem. Phys.*, 1953, **21**, 66). There does, however,

appear to be a correlation between the wave-length of maximum absorption of the charge-transfer spectrum of the complex and the wave-length of the longest ultra-violet absorption maximum of the component alkylaniline for all the *s*-trinitrobenzene interactions studied in the present work (Table 9).

TABLE 9.

Base	$\lambda_{max.}$ (base alone in CXA) (mμ)	$\lambda_{max.}$ (complex with *s*-trinitrobenzene in CXA) (mμ)
Aniline	285	390
N-Methylaniline	296	435
N-Ethylaniline	296	445
N-*n*-Doedcylaniline	296	445
NN-Dimethylaniline	298	475
NN-Diethylaniline	304	501
NN-Di-*n*-propylaniline	305	504
NN-Di-*n*-pentylaniline	305	510
NN-Di-*n*-decylaniline	305	510
NNN'N'-Tetramethyl-*p*-phenylenediamine	328	600

CXA = *cyclo*hexane.

Variation of the Solvent.—For the complex *NN*-dimethylaniline–*s*-trinitrobenzene, the effect of changing the solvent from *cyclo*hexane to *n*-hexane is to reduce the association constant from 9·5 to 8·2 l./mole. There is a small alteration in the wave-length maximum of the charge-transfer spectrum, but the intensity of the absorption remains constant within the limits of experimental error. The association constant is the same in *n*-heptane as in *n*-hexane, and decreases in the series of solvents *n*-hexane > decalin > carbon tetrachloride > chloroform > *s*-tetrachloroethane > 1 : 4-dioxan. The association constant of *NN*-dimethylaniline–*s*-trinitrobenzene in chloroform (K = 1·3 l./mole) agrees well with that obtained by Ley and Grau (*Ber.*, 1925, **58**, 1765), namely, K = 1·5 l./mole, though in the present determination particularly dilute solutions had to be used to obtain a linear plot of D/b against D (see above).

Probably the most important cause of variation of association constant with solvent is the competition by the solvent for complex formation. *cyclo*Hexane, which is reported to form a complex with iodine (Hastings, Franklin, Schiller, and Matsen, *J. Amer. Chem. Soc.*, 1953, **75**, 2900), may also interact with *s*-trinitrobenzene and, though the association constant will undoubtedly be small, the effect may be significant owing to the large concentration of solvent. There appears to be a difference in the order of effect of a series of solvents on the degree of association of *NN*-dimethylaniline–*s*-trinitrobenzene complexes compared with the effect of the same solvents on the stability of certain iodine complexes (Kortum and Walz, *Z. Electrochem.*, 1953, **57**, 73).

The authors are grateful to Dr. K. T. Hanson for the gift of pure *n*-heptane. One of them (R. F.) acknowledges a grant given by the Department of Scientific and Industrial Research. Some analyses are by Mr. F. C. Hall.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, March 31st,* 1954.]

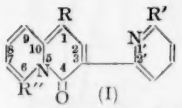
The Lupin Alkaloids. Part XV. Some Derivatives of the 4-Oxo-3-2′-pyridylpyridocoline System.*

By G. R. Clemo, B. W. Fox, and R. Raper.

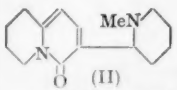
[Reprint Order No. 5269.]

During an examination of possible routes leading to the synthesis of C_{15} lupin alkaloids a number of 4-oxo-3-2′-pyridylpyridocolines and their reduction products were prepared.

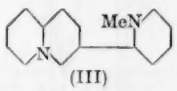
In the investigation of possible synthetic routes to some of the C_{15} lupin alkaloids, we regarded the 4-oxo-3-2′-pyridiylpyridocoline system (I; R = R′ = R″ = H) as a convenient precursor (Clemo, Morgan, and Raper, *J.*, 1936, 1025). Its 1-carboxylic ester (I; R = CO_2Et, R′ = R″ = H) has already been employed by various workers (see Manske and Holmes, "The Alkaloids," Academic Press Inc., New York, Vol. III, pp. 160 *et seq.*). The ethoxycarbonyl group is lost when this base is heated with 2N-hydrochloric acid, giving 4-oxo-3-2′-pyridylpyridocoline (I; R = R′ = R″ = H) (cf. Galinovsky and Kainz, *Monatsh.*, 1947, **77**, 137). Catalytic reduction of the methiodide of this, with Raney nickel and diethylamine (cf. Barltrop and Taylor, *J.*, 1951, 108), gave a colourless solid, five molecules of hydrogen being taken up. Since this product has lost the yellow colour and fluorescence characteristic of the pyridocoline system (cf. Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681), and has an ultra-violet absorption spectrum closely resembling that of 6-methyl-2-pyridone (Fig. 1), it is presumably the piperidyl-tetrahydro-compound (II). Octahydro-4-oxopyridocoline,



(I)



(II)



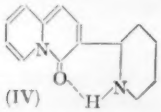
(III)

reduced to norlupinane by lithium aluminium hydride, was obtained as a by-product. Prolonged hydrogenation of the base (II) in acetic acid over platinic oxide gave a viscous oil which gave analytical figures agreeing with those for octahydro-3-2′-*N*-methylpiperidyl-4-oxopyridocoline and was reduced by lithium aluminium hydride to a sparteine-like base, octahydro-3-2′-*N*-methylpiperidylpyridocoline (III). This structure was proposed by Marion and Fenton (*J. Org. Chem.*, 1948, **13**, 780) for the alkaloid pusilline, and our product may contain the externally compensated form of this, together with diastereoisomers. Work is being continued on this substance.

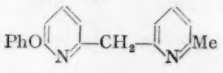
4-Oxo-3-2′-pyridylpyridocoline (I; R = R′ = R″ = H) was hydrogenated in ethanol over platinic oxide at atmospheric temperature and pressure to a light yellow, fluorescent solid, $C_{14}H_{16}ON_2$. Since this has the characteristics of the pyridocoline system and a similar ultra-violet absorption spectrum (Boekelheide and Lodge, *loc. cit.*) (Fig. 2) it is probably 4-oxo-3-2′-piperidylpyridocoline (IV), the hypsochromic shift being due to the shortening of the conjugated system by hydrogen bonding. In order to synthesise a 6- or 6′-substituted ethyl 4-oxo-3-2′-pyridylpyridocoline-1-carboxylate, it was necessary to examine the preparation of suitably 6-substituted ethyl 2-pyridylacetates. We were unable to induce 2-hydroxy-6-methylpyridine to react with phenyl-lithium. 2-Chloro- and 2-bromo-6-methylpyridine (Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 232) were converted into the hitherto unknown 2-methoxy-6-methylpyridine; this did not condense with benzaldehyde, and, when it was treated successively with phenyl-lithium and solid carbon dioxide, unchanged material, 2-hydroxy-6-methylpyridine, and a white solid were obtained. The last has an ultra-violet absorption spectrum greatly resembling those of 2-pyridone and its *N*-methyl derivative and gives a strong van der Moer reaction, and appears therefore to be a hydroxylated 1 : 6-dimethyl-2-pyridone. The possibility of its being the isomer 2-methoxy-6-methylpyridine *N*-oxide was eliminated by preparing it by Murakami and Matsumura's method (Jap. P., 177,949/1949; *Chem. Abs.*, 1951, **45**,

* Part XIV, *J.*, 1949, 663.

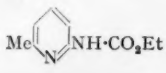
7603). The substances differ markedly. Our product is also different from 4-hydroxy-1 : 6-dimethyl-2-pyridone (Arndt, Eistert, Scholtz, and Aron, *Ber.*, 1936, **69**, 2373) which is the only dimethyl-2-pyridone hitherto described.



(IV)



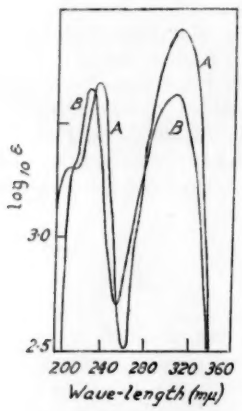
(V)



(VI)

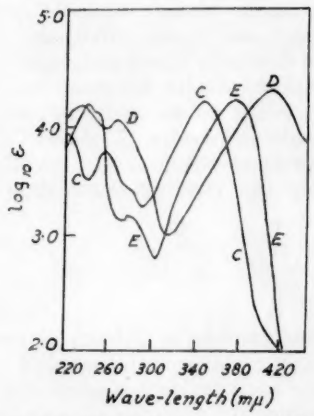
With phenol, 2-bromo-6-methylpyridine gives the 2-phenoxy-derivative but application of the Woodward and Kornfeld process for its conversion into the acetate (*Org. Synth.*, **29**, 44) gave unchanged material, phenol, 2-hydroxy-6-methylpyridine, and an oil which gives a monopicrate and has an ultra-violet absorption spectrum almost identical with that of 2-methyl-6-phenoxypyridine (Fig. 3). Analyses of the base and picrate suggest the molecular formula $C_{18}H_{16-18}ON_2$, and it is probably the bis-derivative (V).

FIG. 1.



A, The compound (II).
B, 6-Methyl-2-pyridone.

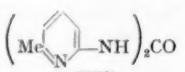
FIG. 2.



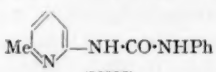
C, 3-2′-Piperidylpyridocoline (IV).
D, The base (I, R = R′ = R″ = H).
E, Octahydro-4-oxopyridocoline.

This structure accounts for the similarity of absorption spectra since the methylene bridge between the two rings prevents conjugation of their double bonds; it accounts also for the formation of only a monopicrate [Renshaw and Conn (*J. Amer. Chem. Soc.*, 1937, **59**, 297) showed that 2-phenoxypyridine was a weak base which did not form salts] and the formation of phenol as a by-product.

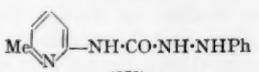
When the product of the action of phenyl-lithium on 2-amino-6-methylpyridine was treated with solid carbon dioxide or ethyl carbonate *N*-(6-methyl-2-pyridyl)urethane (VI) was produced. This forms an azeotrope with the 6-amino-2-picoline, and in an attempt to distil the mixture at a higher pressure a vigorous reaction took place, giving the urea



(VII)



(VIII)

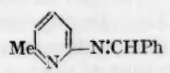


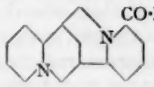
(IX)

(VII). With aniline this urethane gave the corresponding known urea (VIII) (Feist, Awe, and Kublinski, *Arch. Pharm.*, 1936, **274**, 419), and this with phenylhydrazine gave the phenylsemicarbazide (IX), a reaction similar to that discovered by Camps (*ibid.*, 1902, **240**, 350) for 2-pyridylurethane.

Adams and Schrecker (*J. Amer. Chem. Soc.*, 1949, **71**, 1188) claim that 2-acetamido-6-methylpyridine condenses with benzaldehyde to give a stilbazole, but we were unable to repeat their work, and obtained results resembling those of Feist and his co-workers (*loc.*

cit.) who state that the products are amorphous and consist largely of the Schiff's base (X) formed by elimination of the acetyl group, With phenyl-lithium the acetyl group is removed as acetophenone, 6-amino-2-picoline being simultaneously produced.

(X) 

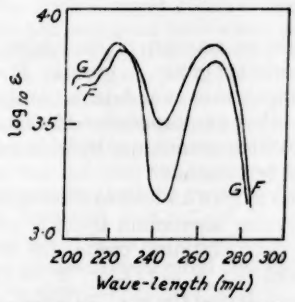


(XI)

Oxidising 2-amino-6-methylpyridine with Caro's acid gave the nitro-compound which did not condense satisfactorily with benzaldehyde, almost the whole being recovered unchanged; by Woodward and Kornfeld's process, apart from unchanged material, only a small amount of 6-chloro-2-picoline was obtained, probably formed by displacement of the nitro-group by the action of the alcoholic hydrogen chloride used in the " esterification " stage.

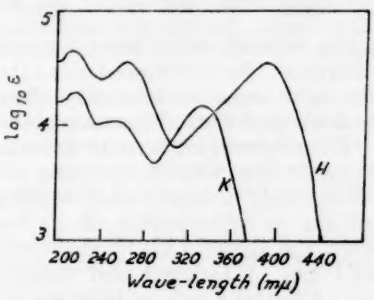
When the Woodward–Kornfeld process was applied to 2 : 6-lutidine, however, ethyl 6-methyl-2-pyridylacetate was obtained. This condensed with ethyl orthoformate to give ethyl 6 : 6′-dimethyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (I; R = CO_2Et, R′ = R″ = Me) only one of the methyl groups of which condensed with benzaldehyde, and since

FIG. 3.



F, 6-*Methyl*-6′-*phenoxydi*-2-*pyridylmethane* (V).
G, 2-*Methyl*-6-*phenoxypyridine*.

FIG. 4.

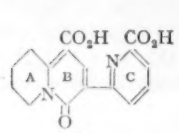


H, *The ester-acid* (I; R = CO_2Et, R′ = CO_2H, R″ = H).
K, *The diacid* (XII).

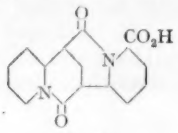
that in the 6′-position is, in effect, that of a 6-substituted 2-methylpyridine, it would be expected to react rather than the 6-methyl group. For our purposes, however, it would have been better to have the 6′-monomethyl product. We therefore condensed ethyl β-hydroxy-α-2-pyridylacrylate (Clemo, Morgan, and Raper, *J.*, 1937, 965) with ethyl 6-methyl-2-pyridylacetate, which could lead to either (I; R = CO_2Et, R′ = Me, R″ = H) or (I; R = CO_2Et, R′ = H, R″ = Me). The alternative product was produced when ethyl β-hydroxy-α-(6-methyl-2-pyridyl)acrylate was condensed with ethyl 2-pyridylacetate. One of these substances melted at 139—140°, the other at 142—143°, but the crystalline forms are different, and only the substance prepared from ethyl β-hydroxy-α-2-pyridylacrylate condenses with benzaldehyde. This substance is therefore the desired product (I; R = CO_2Et, R′ = Me, R″ = H).

Decarboxylation of this isomer gave the compound (I; R = R″ = H, R′ = Me), and its benzylidene derivative similarly gave (I; R = R″ = H, R′ = ·CH:CHPh). When attempts were made to oxidise the 6′-methyl ester or its benzylidene derivative with permanganate under a variety of conditions, the only recognisable oxidation product was benzoic acid. With selenium dioxide at 155°, however, the ester gave a mixture of ethyl 6′-carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (I; R = CO_2Et, R′ = CO_2H, R″ = H) and the corresponding 6′-aldehyde. The 6′-amide was obtained by successive treatment of the acid with thionyl chloride and ammonia, but failed to undergo either the Hofmann or the Curtius reaction. Since the latter reaction proceeds smoothly with lupininhydrazide (Clemo, Ramage, and Raper, *J.*, 1931, 3190) we considered that we might apply it satisfactorily to the hydrazide (XI) of sparteine-15-carboxylic acid, which could

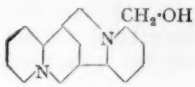
be obtained from (I; R = CO_2Et, R′ = CO_2H, R″ = H) by reductive cyclisation and subsequent reduction of the two carbonyl groups. Before the carboxy-ester could be successfully reduced catalytically residual traces of selenium had to be removed by shaking it with Raney nickel, but it then absorbed 3 mols. of hydrogen at ordinary temperature and pressure over Adams catalyst, giving the diacid (XII). During this process the yellow colour and fluorescence characteristic of the pyridocoline system were lost (see Fig. 4), indicating that the hydrogen had been taken up by ring A since a similar effect was observed by Boekelheide and Lodge (*loc. cit.*) in the reduction of methyl 4-oxopyridocoline-carboxylate to the 6 : 7 : 8 : 9-tetrahydro-compound. A similar shift of absorption bands in the ultra-violet absorption spectra of the two compounds takes place during the reduction and hydrogenolysis. Further catalytic reduction of the diacid (XII) resulted in an uptake of 7 mols. of hydrogen, giving a colourless resin, corresponding in analysis to 10 : 17-dioxosparteine-15-carboxylic acid and soluble in sodium carbonate solution, but it



(XII)



(XIII)



(XIV)

could not be reduced with lithium aluminium hydride on account of its insolubility in suitable solvents. We therefore esterified the second carboxyl group, to give (I; R = R′ = CO_2Et, R″ = H) and, after removal of selenium, hydrogenation over Adams catalyst then gave an oil whose analytical figures suggested it was ethyl dioxosparteine-15-carboxylate (XIII). This product gave no solid derivatives, and lithium aluminium hydride reduction gave no product from which a crystalline picrate could be obtained.

The 6′-aldehyde mentioned above might be expected to give 15-hydroxymethyl-10 : 17-dioxosparteine on hydrogenation, and subsequent lithium aluminium hydride reduction would yield the alcohol (XIV). On hydrogenation over platinum oxide, the aldehyde absorbed 1 mol. of hydrogen and yielded the alcohol (I; R = CO_2Et, R′ = CH_2·OH, R″ = H). A further 8 mols. of hydrogen were taken up during the next 30 hours, giving a pale yellow, viscous oil in low yields (10—15%), not imporved by use of Raney nickel at high temperatures and pressures or copper chromite.

Work is being pursued on these and other lines with the object of synthesing alkaloids of this series whose constitutions need this confirmation.

Experimental

Ethyl 4-Oxo-3-2′-pyridylpyridocoline-1-carboxylate (I; R = CO_2Et, R′ = R″ = H).—Ethyl 2-pyridylacetate (32 g.), ethyl orthoformate (30 g.), and acetic anhydride (36 ml.) were heated on a water-bath for 14 hr., and the product was poured into potassium carbonate (40 g.) in warm water (50 ml.). The oily base was extracted with chloroform, dried ($MgSO_4$), and distilled (yield, 23 g.; b. p. 250—260°/1 mm., m. p. 126°). Light absorption in EtOH: max. at 2650 (ε 22,400) and 4000 Å (ε 21,125).

Attempts were made to reduce the substance by placing it in a Soxhlet thimble through which an ethereal solution of 6 equivs. of lithium aluminium hydride refluxed. The complex mixture of products was separated by chromatography on alumina, ten bands being obtained, from one of which a *substance* forming yellow prisms, m. p. 140° (decomp.), was obtained (Found: C, 70·0, 70·0; H, 5·5, 6·1. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·25%).

4-Oxo-3-2′-pyridylpyridocoline (I; R = R′ = R″ = H).—The above ester (10 g.) was refluxed for 5 hr. with 2N-hydrochloric acid (30 ml.), and the cooled solution basified with 30% aqueous potassium hydroxide; *4-oxo-3-2′-pyridylpyridocoline* separated (7·5 g.). It crystallised from water in shining yellow plates, m. p. 111—112° after loss of water at 100° (Found: C, 70·3; H, 5·0; N, 11·7. $C_{14}H_{10}ON_2,H_2O$ requires C, 70·0; H, 5·0; N, 11·65%. Found, in the anhydrous base: C, 75·8; H, 4·9. $C_{14}H_{10}ON_2$ requires C, 75·5; H, 4·5%). The substance gives a deep crimson colour with a dilute solution of chromic oxide in concentrated sulphuric acid. Light absorption: Max. at 2350 (ε 14,850), 2675 (ε 10,810), and 4125 Å (ε 19,360).

The *methiodide* was obtained by heating the hydrated base (13·5 g.), methyl iodide (10·8 ml.),

and acetone (10 ml.) in a sealed tube in the water-bath for 1 hr. The product was triturated with acetone (20 ml.), collected, and crystallised from acetone in yellow plates with a violet reflex, m. p. 253—254° (Found: C, 49·1; H, 3·8; N, 7·8. $C_{14}H_{10}ON_2.CH_3I$ requires C, 49·5; H, 3·6; N, 7·7%).

6 : 7 : 8 : 9-*Tetrahydro*-3-(1-*methyl*-2-*piperidyl*)-4-*oxopyridocoline*.—The above methiodide (15·2 g.), diethylamine (10 ml.), and Raney nickel (W2) in methanol (150 ml.) were hydrogenated at 170°/160 atm. for 4½ hr. The catalyst and solvents were removed, the residue was basified with potassium carbonate and extracted with chloroform, and the extract dried and distilled. *4-Oxonorlupinane* (0·6 g.), b. p. 100—103°/2 mm. (Found: C, 70·6; H, 9·9; N, 9·4. $C_9H_{15}ON$ requires C, 70·6; H, 9·8; N, 9·15%), passed over first, followed by a liquid *base* (6·5 g.), b. p. 178—182°/1 mm., which readily solidified and crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 67—68° (Found: C, 73·1; H, 8·65. $C_{15}H_{22}ON_2$ requires C, 73·2; H, 8·95%). The *methiodide* forms colourless needles (from acetone), m. p. 211—212° (Found: C, 49·6; H, 6·7; N, 7·2. $C_{15}H_{22}ON_2.CH_3I$ requires C, 49·5; H, 6·4; N, 7·2%). The styphnate, yellow prisms (from methanol), has m. p. 136—138°. The oxonorlupinane, reduced with lithium aluminium hydride, furnished a base, b. p. 80—85°/18 mm., which gave a picrate, m. p. 211° (norlupinane picrate, 212°).

Octahydro-3-(1-*methyl*-2-*piperidyl*)-4-*oxopyridocoline* (II).—The above tetrahydro-base (1 g.) in acetic acid (40 ml.) was hydrogenated at 100 lb./sq. in. and room temp. over platinum oxide for 30 hr. Solvent and catalyst were removed, the residue was basified with potassium carbonate and extracted with ether, and the dried extract was distilled, giving a pale yellow *octahydro*-base (0·4 g.), b. p. 172—174°/0·1 mm. (Found: C, 72·2; H, 10·8. $C_{15}H_{26}ON_2$ requires C, 72·0; H, 10·4%).

Octahydro-3-(1-*methyl*-2-*piperidyl*)*pyridocoline* (III).—The octahydro-4-oxo-compound (0·3 g.) in dry ether (5 ml.) was added carefully to lithium aluminium hydride (0·2 g.) in ether (10 ml.) and refluxed for 18 hr. Water and then sulphuric acid (10 ml.; 20%) were added, the aqueous layer was basified with 30% aqueous potassium hydroxide and extracted with chloroform, and the dried extract distilled, giving a pale yellow *product*, b. p. 114—116°/0·2 mm. (Found: C, 76·6; H, 12·0; N, 11·3. $C_{15}H_{28}N_2$ requires C, 76·3; H, 11·8; N, 11·8%). When methyl iodide was added to an ethyl acetate solution of the base, an oil and a solid were obtained. The latter recrystallised from ethyl acetate in colourless prisms, m. p. 258—260°. The perchlorate and picrate were oils.

4-Oxo-3-2′-piperidylpyridocoline.—4-Oxo-3-2′-pyridylpyridocoline (2·5 g.) in ethanol (50 ml.) and hydrochloric acid (1 drop) was hydrogenated at room temp. and pressure for 36 hr., 720 ml. (3 mols.) being absorbed. Working up as usual gave the *piperidyl* compound as a yellow syrup (b. p. 210—220°/2 mm.) which soon solidified and crystallised from light petroleum (b. p. 40—60°) in cream-coloured needles, m. p. 76—77° (Found: C, 74·2; H, 7·4. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·0%). The *picrate* softens at 164° and melts at 174—175° (Found: C, 53·0; H, 4·2; N, 14·8. $C_{14}H_{16}ON_2.C_6H_3O_7N_3$ requires C, 52·5; H, 4·2; N, 15·3%); the *N-methyl* derivative *hydriodide* forms colourless needles, m. p. 235°, from acetone (Found: C, 48·4; H, 4·9. $C_{15}H_{19}ON_2I$ requires C, 48·6; H, 5·1%).

4-Oxo-3-(1-methyl-2-piperidyl)pyridocoline.—4-Oxo-3-2′-piperidylpyridocoline methiodide (0·5 g.) was warmed for ½ hr. on the water-bath with sodium hydroxide (30%; 5 ml.), and the product was extracted with chloroform and distilled. An oily *base* (0·05 g.; b. p. 160—170°/1 mm.) was obtained which solidified and recrystallised from light petroleum (b. p. 60—80°) in yellow needles, m. p. 89—90° (Found: N, 11·7. $C_{15}H_{18}ON_2$ requires N, 11·6%). The *picrate* forms yellow needles, m. p. 195—196°, from methanol (Found: N, 15·1. $C_{15}H_{18}ON_2.C_6H_3O_7N_3$ requires N, 14·9%).

2-Chloro-6-methylpyridine.—The following method is better than that of Seide (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216). 2-Hydroxy-6-methylpyridine (Adams and Schrecker, *J. Amer. Chem. Soc.*, 1949, **71**, 1188) (10 g.) and phosphorus oxychloride (20 g.) were heated at 150° for 18 hr., the product was basified with 20% aqueous potassium hydroxide and extracted with chloroform, the extract dried, and the solvent removed, giving the base as an oil (9·3 g.), b. p. 75—80°/10 mm.

2-Bromo-6-methylpyridine was prepared in the same way as 2-bromopyridine (Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 232). It is a colourless sweet-smelling oil, b. p. 80—90°/10 mm. Willink and Wibaut (*Rec. Trav. chim.*, 1934, **53**, 417) give b. p. 205—207°/772 mm. It gave a picrate (yellow needles from methanol), m. p. 163°, and a hydrobromide (colourless plates from acetone), m. p. 168—170° with a change of crystal shape between 135° and 140°.

2-Methoxy-6-methylpyridine.—Sodium (8 g.) was dissolved in methanol (100 ml.) and the

solution evaporated to a syrup which was heated with 2-bromo-6-methylpyridine (50 g.) in an autoclave at 200° for 1 hr. The reaction mixture was poured into water, the liberated base extracted with chloroform, the extract dried, the solvent removed at 70—80°, and the residue fractionated through a 7″ Vigreux column, giving the *methoxy*-base (34·3 g.), b. p. 156°/759 mm., n_D^{20} 1·5590 (Found: C, 67·95; H, 7·9. C_7H_9ON requires C, 68·3; H, 7·3%), having a fruity smell and giving a picrate, yellow needles (from ethanol), m. p. 132—133°.

When 2-methoxy-6-methylpyridine was added to phenyl-lithium in ether, the red complex poured on solid carbon dioxide, and the colourless product treated with ethanolic hydrogen chloride as in Woodward and Kornfeld's process, a product was obtained which was fractionated into unchanged material (60%), 2-hydroxy-6-methylpyridine (10%), m. p. and mixed m. p. 159°, and a white *substance* (20%; obtained by sublimation of the fraction, b. p. 125°/1 mm.), m. p. 161°, depressed to 139° by admixture with 2-hydroxy-6-methylpyridine (Found: C, 60·6; H, 6·5; N, 9·8. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%).

2-*Methoxy*-6-*methylpyridine* N-*Oxide*.—2-Methoxy-6-methylpyridine (4·75 g.) was added slowly to ice-cold hydrogen peroxide (4·6 ml.; 100-vol.), After 10 min. finely powdered phthalic anhydride (5·7 g.) was added and the whole stirred at 0° for 30 min., the pale yellow solution becoming more viscous. Hydrochloric acid (30 ml.; 10%) was added, phthalic acid filtered off after 20 min., the filtrate evaporated to dryness, and the residue dissolved in ethanol, filtered, again evaporated, and recrystallised from acetone, giving the *hydrochloride* (5·9 g.), m. p. 134°, of the *N*-oxide (Found: C, 47·9; H, 5·9. $C_7H_9O_2N$,HCl requires C, 47·9; H, 5·7%). This reacted exothermally in methanol with freshly precipitated silver oxide. After filtration and evaporation the residue crystallised from light petroleum (b. p. 60—80°), giving the N-*oxide* as colourless prisms, m. p. 55—56° (Found: N, 10·0. $C_7H_9O_2N$ requires N, 10·1%).

6-*Methyl*-2-*phenoxypyridine*.—The following modification of Renshaw and Conn's method (*loc. cit.*) was used. 6-Chloro-2-picoline (9 g.) and phenol (20 g.) were heated for 14 hr. at 180° in sealed tubes. The product was poured into water (20 ml.), potassium hydroxide solution (20 ml.; 20%) was added, and the whole steam-distilled. The distillate was extracted with ether, and the extracts were dried and fractionated through a 7″ Vigreux column, giving 6-*methyl*-2-*phenoxypyridine* (9 g.), b. p. 140°/15 mm., 242—245°/750 mm., n_D^{19} 1·5760 (Found: C, 78·1; H, 6·1. $C_{12}H_{11}ON$ requires C, 77·85; H, 5·95%). Light absorption: max. at 2250 (ε 7219), 2700 Å (ε 5946). When Woodward and Kornfeld's procedure was applied to this base (13·5 g.) the products were phenol (2·1 g.), unchanged material (2·9 g.), and a pale yellow viscous *substance* (5·1 g.), b. p. 190—195°/0·2 mm. (Found: C, 78·3; H, 6·1; N, 10·1%; *M*, determined from the light absorption of picrate, 271. $C_{18}H_{16}ON_2$ requires C, 78·3; H, 5·8; N, 10·1%; *M*, 276). The *picrate* forms yellow needles, m. p. 135—136°, from ethanol (Found: C, 57·2; H, 4·3; N, 14·3. $C_{18}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 57·0; H, 3·8; N, 13·9%).

2-*Amino*-6-*methylpyridine*.—The preparation of this base has been described by Seide (*J. Russ. Phys. Chem. Soc.*, 1918, **50**, 534) but the yield can be improved as follows. Sodium (50 g.) was added to liquid ammonia (750 ml.) containing ferric nitrate (0·3 g.) in a lagged flask, and the excess of ammonia allowed to evaporate. Freshly distilled 2-methylpyridine (200 g.; b. p. 127—128°) in pure xylene (300 ml.) was added carefully and the whole refluxed and stirred at 135—140° for 5 hr., and allowed to cool slowly overnight. Ice was added to decompose sodamide, excess of hydrochloric acid added, the xylene layer removed, and the base liberated by sodium hydroxide, extracted with ether, dried, and distilled through a 7″ Vigreux column (138 g.; b. p. 100—105°/15 mm., m. p. 40—41°).

6-*Methyl*-2-*pyridylurethane* (VI).—2-Amino-6-methylpyridine (20 g.) in dry ether (20 ml.) was added slowly to freshly prepared sodamide (7·2 g.) in ether (30 ml.); after 14 hr., ether (200 ml.) was added and the whole refluxed for 10 hr. Ethyl carbonate (11 g.) in ether (20 ml.) was added at such a rate as to maintain gentle reflux, and after boiling for a further ½ hr. the solution was cooled to 0° and acidified to Congo-red. The ethereal layer was removed, the aqueous liquid basified with sodium hydrogen carbonate and extracted with ether, and the extract dried; after removal of solvent, distillation gave the aminopicoline (6·4 g.) and the *urethane* (12·3 g.), b. p. 115—117°, m. p. 55—56° (from dilute ethanol) (Found: C, 59·9; H, 6·9; N, 15·3. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·7; N, 15·55%). The *picrate* forms golden-yellow plates, m. p. 131°, from ethanol (Found: C, 43·7; H, 3·9; N, 17·2. $C_9H_{12}O_2N_2,C_6H_3O_7N_3$ requires C, 44·0; H, 3·7; N, 17·1%).

NN′-*Di*-(6-*methyl*-2-*pyridyl*)*urea* (VII).—The above urethane (VI) (3·6 g.) and 2-amino-6-methylpyridine (2·16 g.) were heated to boiling, whereupon reaction occurred exothermally. After cooling, the *urea* was obtained as colourless needles (4·8 g.), m. p. 189—190°, from benzene (Found: C, 64·3; H, 6·05; N, 22·9. $C_{13}H_{14}ON_4$ requires C, 64·4; H, 5·8; N, 23·15%).

N-(6-*Methyl*-2-*pyridyl*)-N′-*phenylurea* (VIII).—The urethane (VI) (1 g.) was boiled with aniline (0·6 g.), and the product crystallised from benzene, giving the urea as colourless needles (1·25 g.), m. p. 186—187° (Found: C, 69·0; H, 6·0. Calc. for $C_{13}H_{13}ON_3$: C, 68·7; H, 5·7%). Feist gives m. p. 186°.

4-(6-*Methyl*-2-*pyridyl*)-1-*phenylsemicarbazide*.—(*a*) The dipyridylurea (VII) and phenylhydrazine (equiv. quantities) were refluxed for 16 hr. in dry pyridine. The solution was added to 3N-sodium carbonate; the precipitated *semicarbazide*, crystallised from dilute ethanol, had m. p. 162—163°, contracting at 100° (25%) (Found: C, 59·8; H, 6·2; N, 21·8. $C_{13}H_{14}ON_4,H_2O$ requires C, 60·0; H, 6·2; N, 21·5%).

(*b*) *N*-(6-Methyl-2-pyridyl)urethane (1 g.) and phenylhydrazine (0·6 g.), refluxed for 30 min., gave the same product (1 g.), m. p. and mixed m. p. 162—163°.

Ethyl 6-*methyl*-2-*pyridylacetate* was prepared from 2 : 6-lutidine by the Woodward–Kornfeld procedure in 40% yield. It is a pale yellow liquid, b. p. 87—89°/0·2 mm. (Found: C, 67·5; H, 7·5; N, 8·2. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3; N, 7·8%). The *picrate* forms yellow plates (from ethanol), m. p. 105—106° (Found: C, 47·5; H, 4·2; N, 14·2. $C_{10}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 47·0; H, 3·9; N, 13·7%).

Ethyl 6 : 6′-*Dimethyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—Ethyl 6-methyl-2-pyridylacetate (8 g.), ethyl orthoformate (7·5 g.), and acetic anhydride (9·3 ml.) were refluxed for 3 hr., the anhydride was removed, and the residue distilled. The fraction of b. p. 220—230°/0·2 mm. (4·63 g.) rapidly solidified and from light petroleum (b. p. 100—120°) yielded the *pyridocoline* as yellow needles, m. p. 119—120° (Found: C, 70·8; H, 5·7; N, 9·0. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%).

This ester (2 g.), benzaldehdye (12 ml.), and acetic anhydride (20 ml.) were refluxed for 66 hr. Benzaldehyde was removed in steam, and on cooling the residual oil solidified and was taken up in hot acetone and boiled with charcoal and filtered. The 6′-*styryl* derivative separated on cooling in orange plates (0·4 g.), m. p. 193—194° (Found: C, 76·1; H, 5·7; N, 7·0. $C_{26}H_{22}O_3N_2$ requires C, 76·1; H, 5·4; N, 6·8%).

Ethyl β-*Hydroxy*-α-2-*pyridylacrylate*.—The following improved method was used. Potassium (10·5 g.) was dissolved in dry ethanol (37·7 ml.) and ether (100 ml.); ether (150 ml.) was added, and a mixture of ethyl 2-pyridylacetate (42 g.) and ethyl formate (21 g.) run into the ice-cooled solution. A solid separated which soon dissolved on shaking. After 40 hr. a pale cream-coloured solid had been deposited. Water (100 ml.) was added, the ether layer removed, and the aqueous solution just acidified to Congo-red and at once basified with potassium carbonate. The solid was extracted with chloroform, the solvent removed, and the residue crystallised from light petroleum (b. p. 60—80°) in almost colourless needles (38 g.), m. p. 99°.

Ethyl 6′-*Methyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—The above hydroxymethylene compound (10 g.), ethyl 6-methyl-2-pyridylacetate (9·4 g.), and acetic anhydride (25 ml.) were refluxed for 1½ hr. Acetic anhydride was removed in a vacuum, and the resulting liquid poured into a solution of potassium carbonate (32 g.) in water (150 ml.) at 100°. The cooled suspension was extracted with chloroform and dried, and the *pyridocoline* left on evaporation crystallised in yellow needles (14·8 g.), m. p. 142—143° (Found: C, 70·3; H, 5·5; N, 8·9. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·3; N, 9·1%. Light absorption, max. at 2670 (ε 19,600) and 4040 Å (ε = 21,110).

6′-*Methyl*-4-*oxo*-3-2′-*pyridylpyridocoline* was produced when this ester (1 g.) was boiled for 16 hr. with 5N-hydrochloric acid (10 ml.), the mixture basified with 20% potassium hydroxide, and the solid filtered off from the cooled solution and crystallised from water. It forms golden yellow plates with blue-green reflex (0·7 g.), m. p. 101—102° (Found: C, 73·6; H, 5·4; N, 11·6. $C_{15}H_{12}ON_2,\frac{1}{2}H_2O$ requires C, 73·5; H, 5·3; N, 11·4%).

Ethyl β-*Hydroxy*-α-(6-*methyl*-2-*pyridyl*)*acrylate*.—This *ester* was prepared in the same way as the methyl-free compound and forms prisms (m. p. 67—68°) and needles (m. p. 59—60°) from light petroleum (b. p. 60—80°). The forms are interconvertible by crystallisation from this solvent (Found: C, 64·1; H, 6·5; N, 7·0. $C_{11}H_{13}O_2N$ requires C, 63·7; H, 6·3; N, 6·8%).

Ethyl 6-*Methyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—Ethyl β-hydroxy-α-(6-methyl-2-pyridyl)acrylate (1 g.), ethyl 2-pyridylacetate (0·9 g.), and acetic anhydride were refluxed for 2 hr. and worked up as for the 6′-methyl compound. The 6-*methyl* compound forms yellow needles (1·4 g.), m. p. 139—140°, from light petroleum (b. p. 100—120°) (Found: C, 70·1; H, 5·5; N, 9·4%).

Ethyl 4-*Oxo*-3-2′-*pyridyl*-6′-*styrylpyridocoline*-1-*carboxylate*.—Ethyl 6′-methyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (3 g.), benzaldehyde (3 ml.), and acetic anhydride (30 ml.)

were refluxed for 80 hr. and worked up as before. The *product* crystallised from acetone in old-gold needles (1·8 g.), m. p. 174—175° (Found: C, 75·5; H, 5·2; N, 7·1. $C_{25}H_{20}O_3N_2$ requires C, 75·8; H, 5·05; N, 7·1%).

4-Oxo-3-2′-pyridyl-6′-styrylpyridocoline was formed when the ester was boiled for 18 hr. with concentrated hydrochloric acid. Crystallised from ethanol–water, it has m. p. 163—164° (Found: C, 81·3; H, 5·4; N, 8·4. $C_{22}H_{16}ON_2$ requires C, 81·5; H, 4·9; N, 8·6%).

Ethyl 6′-Formyl- and 6′-Carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate.—A finely ground mixture of ethyl 6′-methyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (4·2 g.; dried at 100°/15 mm. for 1 hr.) and freshly sublimed selenium dioxide (3·4 g.) were heated to 155—160°; a vigorous reaction took place, steam being evolved. After 15 min. at this temperature, the cooled residue was triturated with N-hydrochloric acid (100 ml.), then heated to boiling and filtered. Sodium acetate solution (20%) was added to the hot filtrate till a yellow solid separated. The suspension was cooled to 80° and immediately filtered, giving the *formyl* derivative, which crystallised from 1 : 1 light petroleum (b. p. 60—80°)–benzene in yellow prisms (2·5 g.), m. p. 179—180° (Found: C, 67·1; H, 4·5; N, 8·5. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·35; N, 8·7%). It gave a deep red colour with benzidine in glacial acetic acid. The *oxime* was formed when the formyl derivative (1 g.) was boiled for 1 hr. with hydroxylamine hydrochloride (0·25 g.) in pyridine (10 ml.). The pyridine was evaporated in a current of air and the solid residue recrystallised from methanol; it had m. p. 275—277° (0·7 g.) (Found: C, 64·55; H, 4·9. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·45%). The original filtrate from the formyl derivative, on cooling to room temperature, deposited the 6′-carboxylic acid (1·4 g.) which crystallised from water as the *dihydrate*, yellow needles, sintering at 120—125°, m. p. 214—216° (Found: C, 57·45; H, 4·7; N, 7·5. $C_{18}H_{14}O_5N_2,2H_2O$ requires C, 57·45; H, 4·8; N, 7·5%). The anhydrous *acid* was obtained (m. p. 215—216°) by careful heating at 130° (Found: N, 8·3. $C_{18}H_{14}O_5N_2$ requires N, 8·3%). Light absorption: max. at 2150 (ε 44,920), 2650 (ε 37,730), and 3930 Å (ε 37,730). The *diacetate* has m. p. 235—236° (decomp.) (Found: C, 57·4; H, 4·3. $C_{18}H_{14}O_5N_2,2C_2H_4O_2$ requires C, 57·6; H, 4·8%).

Ethyl 6′-Carbamoyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate.—The acid (0·45 g.) was refluxed for ½ hr. with thionyl chloride (3 ml.), and the clear yellow-brown solution evaporated on the water-bath; benzene (2 ml.) was added, and the whole again evaporated. Aqueous ammonia (10 ml.; *d* 0·880) was added, and the *amide* collected and recrystallised from dioxan–water (3 : 2) as yellow needles (0·45 g.), m. p. 265—267° (Found: C, 64·4; H, 4·1. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·45%).

6 : 7 : 8 : 9-Tetrahydro-4-oxo-3-2′-pyridylpyridocoline-1 : 6′-dicarboxylic Acid (XII).—Ethyl 6′-carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate dihydrate (1·1 g.) was suspended in water (50 ml.), and sufficient sodium hydroxide solution (40%) was added dropwise to effect dissolution. The solution was shaken with Raney nickel for 10 min., the nickel filtered off, platinum oxide (0·1 g.) added, and the yellow solution shaken with hydrogen at atmospheric temperature and pressure: 201 ml. were absorbed in 3 hr., the solution becoming bright red and then colourless. The catalyst was removed, and addition of a few drops of 3N-hydrochloric acid precipitated the *tetrahydropyridocoline trihydrate*, which crystallised from water in colourless plates (0·9 g.), m. p. 247—249° (decomp.) (Found: C, 52·3; H, 5·3; N, 7·6. $C_{16}H_{14}O_5N_2,3H_2O$ requires C, 52·2; H, 5·4; N, 7·6%). Light absorption: max. at 2150 (ε 20,100), 2650 (ε 10,000), and 3300 Å (ε 15,010).

10 : 17-Dioxosparteine-15-carboxylic Acid (XIII).—Ethyl 6′-carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate dihydrate (1·5 g.) was shaken in acetic acid (50 ml.) and water (30 ml.) with Raney nickel and filtered. Platinic oxide (0·1 g.) was added, and the whole shaken with hydrogen at atmospheric temperature and pressure for 70 hr., 705 ml. (7 mols.) being absorbed. After removal of catalyst and solvents a white resin remained (1 g.) which distilled at 200—210°/0·2 mm. (Found: C, 63·2; H, 7·4. $C_{16}H_{22}O_4N_2$ requires C, 62·7; H, 7·2%). This *acid* was soluble in cold 20% sodium hydroxide solution, and in sodium carbonate solution with effervescence. No picrate, picrolonate, or styphnate could be prepared.

Diethyl 4-Oxo-3-2′-pyridylpyridocoline-1 : 6′-dicarboxylate.—The dihydrate of the monoethyl ester (2·7 g.) and thionyl chloride (10 ml.) were refluxed for ½ hr., the excess of thionyl chloride removed by evaporation and treatment with benzene, ethanol (10 ml.) was added (much hydrogen chloride was evolved), and the whole refluxed for ½ hr. Excess of ethanol was removed, and the diester liberated with potassium carbonate and extracted with chloroform. Removing the solvent left the *diester*, which solidified and crystallised from light petroleum (b. p. 100—120°) in golden-yellow needles (2·5 g.), m. p. 146—147° (Found: C, 65·6; H, 5·3; N, 8·0. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9; N, 7·65%).

Ethyl 10 : 17-*Dioxosparteine*-15-*carboxylate*.—The above diethyl ester (1 g.) in glacial acetic acid (25 ml.) was shaken for 10 min. with Raney nickel, and the filtered solution was shaken with platinic oxide (0·2 g.) and hydrogen at 100 lb./sq. in. and room temperature for 18 hr., 7 mols. being absorbed. The solvent was removed, the residue basified as above and extracted with chloroform, and the extract distilled, giving the gummy *ester* (0·4 g.), b. p. 210—220°/0·2 mm. (Found : N, 8·4. $C_{18}H_{26}O_4N_2$ requires N, 8·4%). On reduction of this (0·25 g.) with lithium aluminium hydride, a trace of oil (5 mg.), b. p. 150—160°/0·2 mm., which gave neither solid picrate nor picrolonate, and a glass (0·2 g.) were obtained.

Ethyl 6′-*Hydroxymethyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—Ethyl 6′-formyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (0·9 g.) in glacial acetic acid (40 ml.) was shaken with Raney nickel, filtered, and then shaken with platinic oxide (0·2 g.) and hydrogen at room temp. and pressure, 65 ml. (1 mol.) being absorbed in 10 min. The catalyst and solvent were removed, and the residue was basified as above and extracted with chloroform, on removal of which the *hydroxymethyl* compound remained; it crystallised from ethanol in yellow prisms (0·9 g.), m. p. 166—167° (Found : N, 8·8. $C_{18}H_{16}O_4N_2$ requires N, 8·6%).

18-*Hydroxymethyl*-10 : 17-*dioxosparteine* (XIV).—When the preceding hydrogenation was continued for 50 hr., 8 mols. of hydrogen were absorbed and an *alcohol* was obtained as a pale yellow oil (0·1 g.), b. p. 210—220°/0·3 mm. (Found : N, 9·6. $C_{16}H_{24}O_3N_2$ requires N, 9·5%).

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KING'S COLLEGE, NEWCASTLE-UPON-TYNE. [*Received, March 31st,* 1954.]

A Theoretical Investigation of the Chemical Reactivity of Glyoxaline.

By I. M. BASSETT and R. D. BROWN.

[Reprint Order No. 5202.]

From a theoretical investigation of the glyoxaline molecule by the molecular-orbital approximation, undertaken in an attempt to elucidate the orientations observed in electrophilic susbtitutions, it is concluded that electrophilic substitutions in acidic media, such as nitration, bromination, and sulphonation, occur in the glyoxaline molecule itself, or in the glyoxalinium cation. In alkaline solution however the substitution must occur in the glyoxaline anion wherever the substitution occurs preferentially in the 2-position. This mechanism applies to diazonium coupling, and is suggested here for the iodination of glyoxaline.

THE chemistry of glyoxaline and its derivatives has been studied in some detail but hitherto the interpretation of some of the observations has proved difficult. In particular it has been difficult to reconcile the facts that nitration and sulphonation occur exclusively, and bromination preferentially, in the 4-position, while diazonium compounds preferentially attack the 2-position, because these reactions are now recognised to be electrophilic substitutions (Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953, pp. 269, 297). Schofield (*Quart. Reviews*, 1950, **4**, 382) suggested that the difference might arise if the glyoxalinium cation were involved in the nitration (*i.e.*, under strongly acid conditions) while coupling occurred in the uncharged glyoxaline molecule. Dewar (" The Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 193) has also made some theoretical speculations on the reactivity of glyoxaline. A detailed theoretical study has therefore been undertaken of the reactivity of glyoxaline, in terms of the LCAO molecular-orbital procedure.

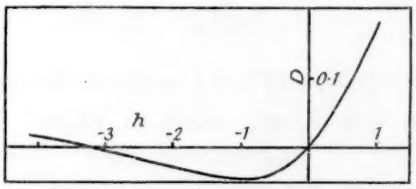
The two nitrogen atoms, and carbon atoms 4 and 5, were taken to be equivalent by symmetry so far as the system of six π-electrons is concerned. This should be an acceptable assumption if the secondary nitrogen is hybridized sp^2, as in pyrrole (Wilcox and Goldstein,

J. Chem. Phys., 1952, **20**, 1656). The resonance integrals of all bonds were taken to have the standard value β, in conformity with previous practice (*e.g.*, Brown, *Quart. Reviews*, 1952, **6**, 63); the carbon atoms were assigned standard coulomb integrals, α, and the nitrogen atoms $\alpha + h\gamma$, h thus being an index of the difference in electronegativity of carbon and nitrogen. All calculations included a standard overlap integral $S = 0{\cdot}250$. Attention was centred on the way in which electron densities and atom-localization energies vary as the relative electronegativity parameter, h, is varied over a wide range of values.

Electron Densities.—The π-electron densities for the various positions in glyoxaline and for various values of h are tabulated in an Appendix. For the discussion of chemical reactivity it is more convenient to consider the quantity $D = q_4 - q_2$ since our main interest is the relative reactivities of the 2- and the 4-position towards electrophilic reagents. Insofar as the charge densities reflect the chemical reactivity, electrophilic substitution would be expected preferentially at position 4 when D is positive, and at position 2 when D is negative. A plot of D as a function of the relative electronegativity parameter, h (Fig. 1), shows that the sign of D changes with varying h: D is positive for positive h, tending to 1 as h tends to $+\infty$, but is negative for h in the range (−3·07, 0), and then positive again for h less than −3·07, passing through a maximum at −7·4, then tending asymptotically to zero as h tends to $-\infty$. Some details of the technique employed for obtaining these data are given in the Appendix.

These results suggest an interpretation of the observed electrophilic substitutions in glyoxaline. The implication is that electrophilic substitutions in acidic media, such as

FIG. 1.



nitration, sulphonation, and bromination, involve a form of glyoxaline such that nitrogen is more electronegative than carbon (*i.e.*, h is positive), while diazonium coupling involves another form of glyoxaline for which nitrogen is less electronegative than carbon [and h lies in the range (−3·07 to 0)]. Now in neutral molecules nitrogen atoms are recognised to be more electronegative than carbon; further, if a nitrogen becomes positively charged, *e.g.*, by protonation, this will enhance its electronegativity and render it still more electronegative than a neutral carbon atom. If however the nitrogen gains a negative charge, such as would arise by the ionization of the proton on a secondary nitrogen atom, this will result in a decrease in electronegativity. Little seems to be known about the magnitude of the change in electronegativity of an atom arising from a change in its formal charge, but it seems possible that a negatively charged nitrogen atom might be *less* electronegative than a neutral carbon atom. The present results imply that diazonium coupling in glyoxaline proceeds through the glyoxaline anion, in which each nitrogen atom carries a formal half electronic charge, and that this is sufficient to make them less electronegative than the ring carbon atoms, corresponding to h in the range −3 to 0. This results in direction of the coupling to the 2-position, whereas nitration occurs through either the neutral glyoxaline molecule or the glyoxalinium cation, for either of which the appropriate value of h is surely positive, resulting in a directive influence favouring the 4-position.

The mechanism of diazonium coupling suggested above has recently been confirmed by kinetic studies (Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937.). A similar mechanism appears to apply for the iodination of glyoxaline in alkaline solution, in which the 2-position is preferentially attacked. Such iodinations are known to proceed by way of electrophilic substitution by I^+ (or its hydrated form H_2OI^+) (Ingold, *op. cit.*, p. 291). The preferential attack on the 2-position indicates that in the alkaline solutions employed the reaction pro-

ceeds through the glyoxaline anion. It is significant also that only glyoxalines with a free imino-group are iodinated. The mechanism suggested by Brunings (*J. Amer. Chem. Soc.*, 1947, **69**, 205), involving initial *N*-iodination and subsequent rearrangement, does not explain why the final product is 2-iodoglyoxaline rather than the 4-isomer.

A further consequence of the above results is that nucleophilic substitution might be expected to be directed in a complementary manner. In the neutral molecule attack would be expected at the 2-position, while the 4-position would be more reactive in the anion. However, the negative charge on the latter would probably completely inhibit any attack by the usual nucleophilic reagents.

Atom Localization Energies.—The values of the atom localization energies, A_e' and A_n', are tabulated in the Appendix for various values of h. The differences, $\Delta A_e' = A_e'(2) - A_e'(4)$, and $\Delta A_n' = A_n'(2) - A_n'(4)$, are plotted against h in Figs. 2 and 3. It emerges that for all values of h, except in the very small range of (0, 0·35), $\Delta A_e'$ is positive (however, values of h greater than +3, for which it appears that $\Delta A_e'$ might become negative, were not investigated because such values do not seem to be physically reasonable,

FIG. 2.

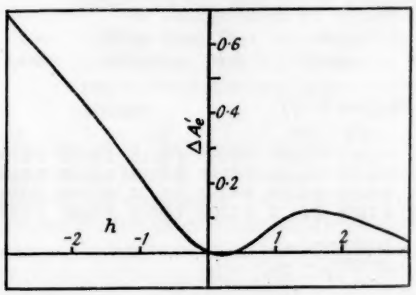
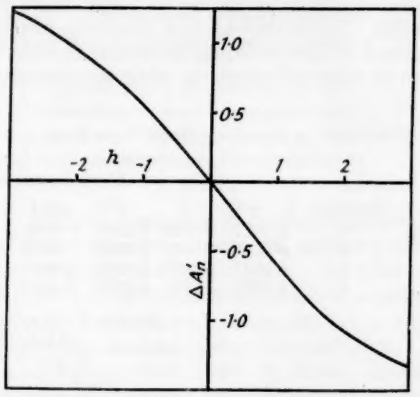


FIG. 3.



even for positively charged nitrogen). Thus for virtually all values of h it is easier to localize two π-electrons at the 4-position than at the 2-position. It is interesting that Dewar (*op. cit.*) deduced precisely the contrary on the basis of symmetry arguments, so the present results demonstrate the dangers of such qualitative speculations about π-electron energies.

For moderate positive values of h, then, both the localization energies and the charge densities indicate that the 4-position would be preferred by electrophilic reagents. The contradiction in the h range (0, 0·35) is trivial because the difference in the two localization energies here is physically quite insignificant, and the actual relative reactivities of the 2- and the 4-position would be expected to lie between those indicated by the localization energies and those indicated by the relative electron densities. So the 4-position would still be expected to be more reactive in this range of h.

Fig. 3 indicates that the nucleophilic localization energies agree with the electron densities, indicating preferential nucleophilic substitution at the 2-position for positive h.

For negative h in the range (−3, 0) the electron densities and localization energies lead to different predictions of orientation for electrophilic substitution. This means (cf. Brown, *loc. cit.*) that the theoretical potential energy curves for the two positions cross somewhere along the reaction co-ordinate. The fact that the charge densities can be made to agree with the observed orientation, and the localization energies cannot, shows that the energy curves cross at a degree of localization between that appropriate for the activated complex and complete localization.

The nucleophilic localization energies are however in agreement with the electron densities for h in the range $(-3, 0)$. Values of h less than -3 are not likely to be physically important, so they do not call for discussion here.

Appendix

Electron densities

Position	h: ∞	1	0	−1	−2	−3	−4	$-\infty$
1	2	1·502	1·200	0·903	0·660	0·489	0·375	0
2	0	0·884	1·200	1·429	1·578	1·675	1·740	2
4	1	1·056	1·200	1·383	1·551	1·674	1·755	2

Calculation of dD/dh *for Location of Maximum.*—Several methods suggest themselves for this purpose. Thus a contour integral expression which may be derived for q can be differentiated under the integral and the resultant integral evaluated numerically. Alternatively the residues at the poles within the contours may be evaluated numerically and summed. Another possibility is to differentiate the secular equations with respect to h, and solve the resultant linear equations in the dc_r/dh by standard methods, making use of the values of the c_r and dx_j/dh. Trials showed that the three methods involved similar computational labour. The method of differentiating the secular equations was preferred, however, because the calculations can be made self-checking, while the alternative methods do not offer this advantage.

h	−1	−4	−5	−6	−7	−7·5	−8
$10^3 dD/dh$	+0·64	−12·15	−5·79	−2·30	−0·45	+0·084	+0·45

Atom localization energies $(-\gamma)$

	Position	h: −3	−1	−0·5	−0·1	0	+0·2	0·5	1	1·5	2	3
A_s	2	0·7827	1·1626	1·2947	1·4058	1·4332	1·4862	1·5566	1·6281	1·6215	1·5558	1·4166
	4	0·0969	0·9475	1·2152	1·3970	1·4332	1·4920	1·5434	1·5482	1·5013	1·4469	1·3838
	2	8·0981	4·4655	3·6502	3·0407	2·8952	2·6135	2·2160	1·6281	1·1433	0·7656	0·3018
A_n	4	6·8663	3·9151	3·3606	2·9812	2·8952	2·7339	2·5173	2·2202	1·9943	1·8297	1·6440

At $h = 0$, $d\Delta A_s'/dh = -0·0690\ (-\gamma)$
$d\Delta A_n'/dh = -0·5979\ (-\gamma)$.

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Steroids and Walden Inversion. Part XIII. The Epimeric Cholest-5-ene-3-carboxylic Acids and the Epimeric Cholestane-3-carboxylic Acids.*

By G. ROBERTS, C. W. SHOPPEE, and R. J. STEPHENSON.

[Reprint Order No. 5223.]

Cholest-5-ene-3β-carboxylic acid (Marker's acid) has been obtained from cholesteryl and *epi*cholesteryl bromide by successive reaction with potassium cyanide and hydrolysis. Cholest-5-ene-3α-carboxylic acid has been prepared by epimerisation of Marker's acid, and by Wieland–Barbier degradation of 3α-cholesterylacetic acid. Cholest-5-ene-3β-carboxylic acid has been converted into cholesteryl cyanide.

Grignard carboxylation of the epimeric cholestanyl bromides gives one and the same cholestane-3β-carboxylic acid, identical with the product obtained by hydrogenation of Marker's acid. Reaction of either of the epimeric cholestanyl bromides with potassium cyanide affords an equilibrium mixture of cholestanyl and *epi*cholestanyl cyanide; the epimeric cholestane-3-carboxylic acids have been transformed into their respective nitriles, which undergo epimerisation to an equilibrium mixture. The cholestane-3-carboxylic acids and methyl esters undergo similar epimerisation.

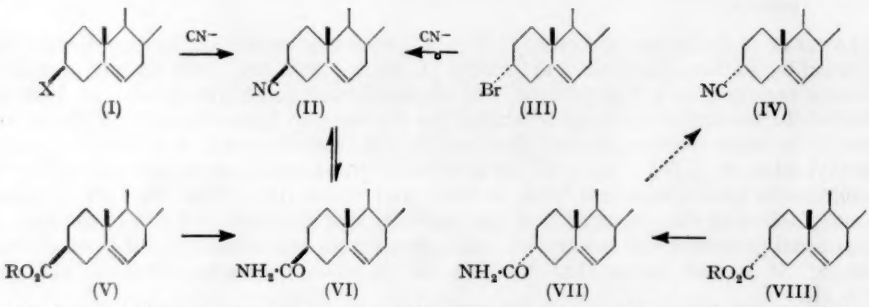
The configuration of Marker's acid as cholest-5-ene-3β-carboxylic acid follows from that established for 3β-cholesterylacetic acid (Shoppee and Stephenson, Part XII*), and has now been confirmed by degradation of the related methyl ketone (as 5α : 6β-dibromide) with perbenzoic acid to cholesteryl acetate.

TREATMENT of cholesteryl chloride (I; X = Cl) with magnesium and carbon dioxide was reported by Marker, Oakwood, and Crookes (*J. Amer. Chem. Soc.*, 1936, **58**, 481) to yield a product regarded as a "*dl*-mixture" of cholest-5-ene-3-carboxylic acids. In 1948 we concluded after careful fractional crystallisation and rigorous chromatography of the methyl ester of the acidic reaction product, that a single acid (Marker's acid), m. p. 220°, $[\alpha]_D$ −10° (methyl ester, m. p. 103°, $[\alpha]_D$ −11°), was formed; this conclusion was also reached in the simultaneous and independent work of Baker and Squire (*ibid.*, 1948, **70**, 4134). Subsequently, following the preparation of the 3-epimeride of Marker's acid and observation of its unusual properties (see below), we repeated our work and confirmed our previous conclusion. It is now shown that Marker's acid is cholest-5-ene-3β-carboxylic acid (V; R = H).

Cholest-5-ene-3β-carboxylic acid (V; R = H) has also been prepared from cholesteryl chloride by treatment with lithium, sodium, or potassium followed by carboxylation with carbon dioxide or diethyl carbonate (B.P. 516,030). Tsuda and Hayatsu (*J. Pharm. Soc. Japan*, 1952, **72**, 1303) claim to have obtained both the epimeric cholest-5-ene-3-carboxylic acids; 3β-cholesterylpyridinium toluene-*p*-sulphonate by pyrolysis at 250—260° gave 4-(3β-cholesteryl)pyridine, which by conversion into the methiodide and oxidation of the quaternary ammonium hydroxide with chromium trioxide–acetic acid at 20—40° gave an acidic product, m. p. 222—225°. Esterification with methanol–sulphuric acid gave 18% of methyl cholest-5-ene-3β-carboxylate, m. p. 100—102° (incorrectly described as the 3α-epimeride). The residual material, by alkaline hydrolysis, gave an acid, m. p. 222—225°, giving 31% of an ethyl ester, m. p. 87—90°, regarded as ethyl cholest-5-ene-3α-carboxylate (although described as the 3β-epimeride) because it gave a small m. p. depression with genuine ethyl cholest-5-ene-3β-carboxylate, m. p. 82—83° (Marker, Oakwood, and Crookes, *loc. cit.*). We have now obtained Marker's acid from cholesteryl bromide (I; X = Br) by successive treatment with potassium cyanide and hydrolysis, and have also prepared its 3-epimeride, cholest-5-ene-3α-carboxylic acid (VIII; R = H), m. p. 155°, $[\alpha]_D$ −40° (methyl ester, m. p. 114°, $[\alpha]_D$ −40°), by Wieland–Barbier degradation of 3α-cholesterylacetic acid (Shoppee and Stephenson, *loc. cit.*), and by epimerisation of Marker's acid with a solution from sodium and diethylene glycol.

* Part XII, *J.*, 1954, 2230.

Relatively few examples of the conversion of secondary alkyl halides into cyanides occur in the literature because replacement is accompanied by preferential dehydrohalogenation; thus, whereas *n*-amyl chloride and sodium cyanide give 95% of *n*-amyl cyanide, *sec.*-amyl chloride gives only 30% of *sec.*-amyl cyanide, and *tert.*-amyl chloride furnishes only olefin(s) (Hass and Marshall, *Ind. Eng. Chem.*, 1931, **23**, 352). *cyclo*Pentyl bromide, however, gives 27% of *cyclo*pentyl cyanide (Rogers and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 843). An unsuccessful attempt to convert cholesteryl toluene-*p*-sulphonate by treatment with potassium cyanide in xylene at 140°, and cholesteryl bromide by fusion with cuprous cyanide at 130°, into cholesteryl cyanide was reported by Baker and Squire (*ibid.*, 1948, **70**, 1487), whilst we independently and unsuccessfully attempted to convert cholesteryl toluene-*p*-sulphonate and cholesteryl bromide into the cyanide by prolonged treatment with silver cyanide in boiling benzene. Recently, ethylene glycol, a more polar medium, has been used as a solvent for sodium cyanide whereby *iso*propyl bromide afforded 39% of *iso*propyl cyanide (Lewis and Susi, *ibid.*, 1952, **74**, 840); by use of potassium cyanide in diethylene glycol at 235° cholesteryl bromide (I; X = Br) yields the cyanide (II) with retention of configuration, as well as cholesta-3 : 5-diene and unidentified products. The configuration of cholesteryl cyanide (II) is proved by its preparation from cholest-5-ene-3β-carboxylic acid (V; R = H) by conversion into the amide (VI) (cf. Baker and Squire, *ibid.*, 1948, **70**, 4134) and dehydration of this with phosphorus oxychloride in toluene at 100°. We regard the reaction (I ⟶ II) as proceeding by a unimolecular substitution (S_N1) involving the cholest-5-en-3β-yl cation (sp^3-hybridisation with a vacant *p* orbital), whose stability is enhanced and whose configuration is preserved by interaction with the π-electrons of the 5 : 6-double bond.



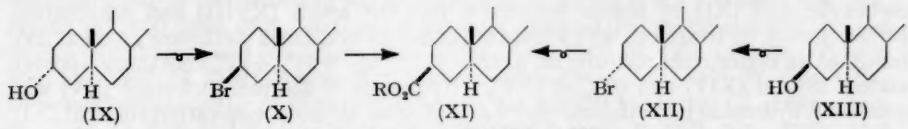
Similar reaction of *epi*cholesteryl bromide (III) gave some cholesteryl cyanide (II) accompanied by much cholesta-3 : 5-diene. We regard the production of cholesteryl cyanide as occurring by direct displacement with inversion of configuration (S_N2); the first unambiguous example of substitution with inversion at $C_{(3)}$ in a Δ^5-steroid has recently been recorded by Shoppee and Stephenson, *loc. cit.*). Much of the *epi*cholesteryl bromide undergoes unimolecular heterolysis to furnish the cholest-5-en-3α-yl cation, whose molecular geometry prevents stabilisation by interaction with the π-electrons of the 5 : 6-double bond; consequently, the cation must acquire stability by rearrangement (Evans and Shoppee, *J.*, 1953, 543) or expulsion of a proton to give cholesta-3 : 5-diene. These results recall those of King and Bigelow (*J. Amer. Chem. Soc.*, 1952, **74**, 6238) who, by treatment of *epi*cholesteryl toluene-*p*-sulphonate with pyridine or piperidine at 100°, obtained cholesterylpyridinium toluene-*p*-sulphonate (8%) or cholesterylpiperidine (10%) by substitution with inversion (S_N2), accompanied by much cholesta-3 : 5-diene (73—75%). We have attempted to prepare *epi*cholesteryl cyanide (IV) from cholest-5-ene-3α-carboxylic acid (VIII; R = H), but the crude amide (VII) proved unexpectedly resistant to dehydration; this will be reinvestigated when larger quantities of material become available.

Cholest-5-ene-3β-carboxylic acid (V; R = H) on treatment with a solution from sodium and diethylene glycol at 235° is epimerised to yield about 5% of cholest-5-ene-3α-carboxylic acid (VIII; R = H), characterised as the methyl ester, and also obtained by Wieland–Barbier degradation of 3α-cholesterylacetic acid. The epimeric acids and esters (V, VIII)

differ in their m. p., optical rotation, and solubilities [(VIII; R = H) is readily soluble in pentane]. We have obtained the ethyl ester (VIII; R = Et) crystalline, m. p. 56—58°; this figure and the m. p. 155° of the pure acid suggest that the acidic material, m. p. 222—225°, and the ethyl ester, m. p. 87—90°, described by Tsuda and Hayatsu (*loc. cit.*) cannot have contained an appreciable proportion of 3α-acid or -ester respectively.

We have also investigated the Grignard carboxylation of the epimeric 3-bromocholestanes; these compounds were carefully purified and were completely free from unsaturated material. 3β-Bromocholestane (X) was prepared from *epi*cholestanol (IX) (Ruzicka, Wirz, and Meyer, *Helv. Chim. Acta*, 1935, **18**, 998), or more conveniently from cholesteryl bromide by hydrogenation with platinum–acetic acid in the presence of perchloric acid; by treatment with magnesium and carbon dioxide it gave uniquely cholestane-3β-carboxylic acid (XI; R = H), identical with the product obtained by catalytic hydrogenation of cholest-5-ene-3β-carboxylic acid (V; R = H) (Marker, Oakwood, and Crookes, *loc. cit.*). In a similar way, cholestanol (XIII) yielded 3α-bromocholestane (XII), which by treatment with magnesium and carbon dioxide gave uniquely the *same* cholestane-3β-carboxylic acid (XI; R = H). The conversion (X) → (XI) thus involves complete overall retention, whilst (XII) → (XI) at some stage involves complete inversion.

During 1948—1951 we attempted unsuccessfully to prepare the acid (XI; R = H) and its 3α-epimeride from the epimeric 3-chlorocholestanes by treatment with magnesium and carbon dioxide; in 1951, however, Squire (*J. Amer. Chem. Soc.*, 1951, **73**, 2586) reported the preparation of cholestanylmagnesium chloride. In a letter dated July 9th, 1951, Dr. E. N. Squire



(IX) (X) (XI) (XII) (XIII)

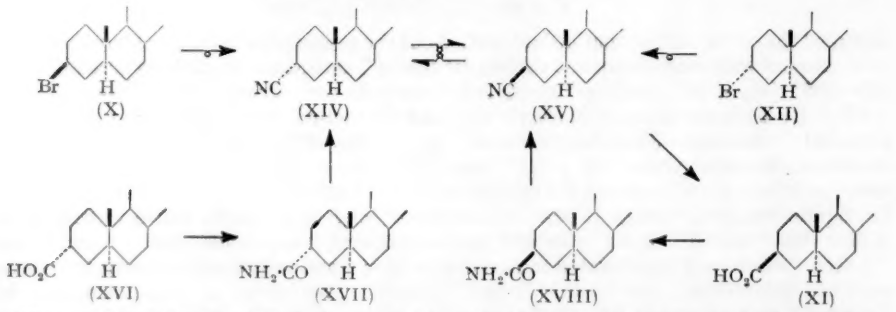
R = H; m. p. 210° ([α]$_D$ +28°)
R = Me; m. p. 52°/69° ([α]$_D$ +27°)

informed the senior author that he had carried out the preparation from 3β-chlorocholestane by treatment with magnesium and carbon dioxide of " cholestane-3β-carboxylic acid," m. p. 206—207°, [α]$_D$ +29°, yielding " methyl cholestane-3β-carboxylate," m. p. 66—67·5°, [α]$_D$ +17°. By hydrogenation of Marker's acid and its methyl ester respectively, Dr. Squire prepared " cholestane-3α-carboxylic acid," m. p. 209—211°, [α]$_D$ +41°, and " methyl cholestane-3α-carboxylate," m. p. 73°, [α]$_D$ +30°; he regarded these pairs of acids and esters as epimeric and assigned configurations on the basis of their optical rotatory powers. Dr. Squire was good enough to send us samples of his four products, which we examined. Whilst his " α-acid " and " α-ester " were saturated compounds, his " β-acid " and " β-ester " contained unsaturated material since they gave yellow colours with tetranitromethane–chloroform; his " α-acid " and " β-acid " gave no m. p. depression, and his " β-ester " melted, not at 66—67·5°, but over a range of 8° (58—66°) either alone or admixed with his " α-ester." Finally, his " α-ester " gave no m. p. depression when mixed with methyl cholestane-3β-carboxylate (XI; R = Me) obtained from pure 3α- or 3β-bromocholestane. We informed Dr. Squire of these facts (letter of July 17th, 1951, acknowledged by letter dated July 23rd, 1951), suggesting that his " β-acid " and " β-ester " are impure * specimens of his " α-acid " and " α-ester "; his subsequent paper (*J. Amer. Chem. Soc.*, 1951, **73**, 5768) makes no reference to these facts and describes his " β-acid " and " β-ester " as homogeneous individuals. It is clear that his configurational assignments are without justification. Analogy suggests that the 17-oxoandrostane-3-carboxylic acid described by Marker *et al.* (*ibid.*, 1936, **58**, 1948) as a mixture of *cis*- and *trans*-stereoiso-

* The probable impurities are cholest-5-ene-3β-carboxylic acid [Marker's acid] (V; R = H) and its methyl ester. 3β-Chlorocholestane, prepared by catalytic hydrogenation of cholesteryl chloride, invariably contains unreduced cholesteryl chloride (cf. Squire, *J. Amer. Chem. Soc.*, 1953, **75**, 493) which must be removed by oxidation with chromium trioxide (Shoppee, *J.*, 1946, 1147) or, better, with perbenzoic acid; this precaution was not taken by Squire. 3β-Chlorocholestane is so considerably more unreactive than cholesteryl chloride toward magnesium that the proportion of unsaturated material in the acid product resulting from carboxylation would be markedly increased.

merides is a single 3β-carboxylic acid, whilst the 17β-hydroxyandrostane-3-carboxylic acid prepared by Baker and Squire (*ibid.*, 1949, **71**, 1383), and the stigmast-5-ene- and stigmastane-3-carboxylic acids described by Squire (*ibid.*, 1953, **75**, 493) are also single 3β-carboxylic acids.

We have also examined the reaction of the epimeric 3-bromocholestanes with potassium cyanide. 3β-Bromocholestane (X) with potassium cyanide in diethylene glycol at 235° gave a 21% yield of a mixture (~2 : 1) of 3β- (XV) and 3α-cyanocholestane (XIV), accompanied by cholest-2-ene. We regard the primary product as 3α-cyanocholestane [XIV; 3α-CN(axial)], formed by bimolecular replacement (S_N2) with inversion, which undergoes partial epimerisation to the more thermodynamically stable 3β-cyanocholestane [XV; 3β-CN(equatorial)] under the conditions of the reaction; some small proportion of 3β-cyanocholestane may arise directly, together with an approximately equal proportion of 3α-cyanocholestane, by the unimolecular mechanism (S_N1), which is probably responsible for the production, following loss of a proton ($E1$), of cholest-2-ene. Similar reaction of 3α-bromocholestane (XII) gave a 5% yield of a mixture (~2 : 1) of 3β-cyanocholestane (XV) [formed by bimolecular substitution with inversion (S_N2)] and 3α-cyanocholestane (XIV) (formed by equilibration), accompanied by much cholest-2-ene [probably formed mainly, but not exclusively, by ionic *trans*-elimination ($E2$)], and unidentified products. The above interpretation is supported by the preparation (i) of 3α-cyanocholestane (XIV), m. p. 168°, $[\alpha]_D$ +21°, from cholestane-3α-carboxylic acid (XVI) (Shoppee and Stephenson, *loc. cit.*) by conversion into the amide (XVII) and dehydration with phosphorus oxychloride, and (ii) of 3β-cyanocholestane (XV), m. p. 152°, $[\alpha]_D$ +28°, from cholestane-3β-carboxylic acid (XI) by similar conversion into the amide (XVIII) and dehydration. Either cyanide by treatment with a trace of potassium cyanide in diethylene glycol at 235° furnished an equilibrium mixture, m. p. 124—127°, $[\alpha]_D$ +26°, +27°, containing approximately 33% of (XIV) and 67% of (XV). Hydrolysis of 3β-cyanocholestane (XV) with potassium hydroxide in diethylene glycol at 235° gave cholestane-3β-carboxylic acid (XI).

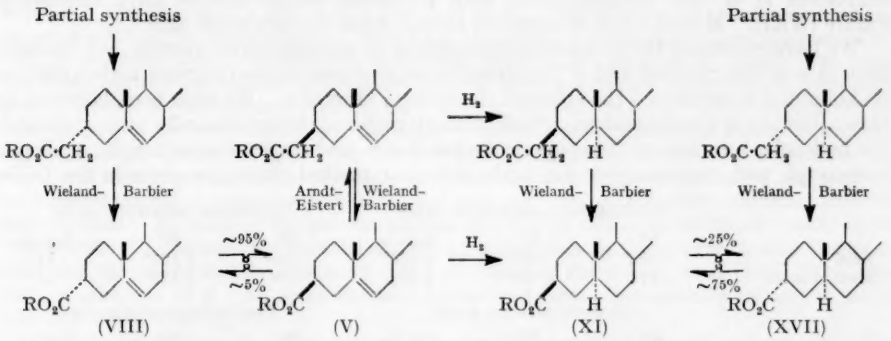


The configurations assigned above to the epimeric cholest-5-ene-3- and cholestane-3-carboxylic acids are established by their relation to the epimeric 3-cholesteryl- and 3-cholestanyl-acetic acids, whose configurations were proved by unambiguous partial syntheses (Shoppee and Stephenson, *loc. cit.*). These relations are summarised in the annexed diagram.

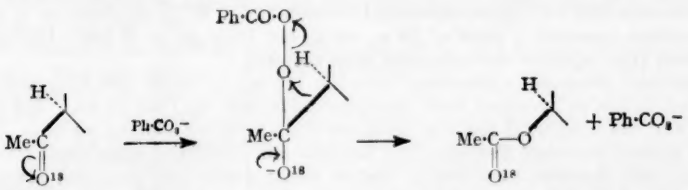
The thermodynamic stabilities of the epimeric pairs (V, VIII) and (XI, XVII) are also consistent. Thus the unsaturated acid (VIII; R = H) and its methyl ester [3α-CO_2R(axial)] * undergo substantially complete epimerisation (~95% conversion) to [V; 3β-CO_2R(equatorial)*]. Likewise, the saturated acid and its methyl ester [XVII: 3α-CO_2R(axial)] undergo similar but less complete epimerisation to [(XI);

* As pointed out previously (Evans and Shoppee, *J.*, 1953, 540; cf. King and Bigelow, *J. Amer. Chem. Soc.*, 1952, **74**, 6241) ring A in cholest-5-ene is a strained chair-form; three contiguous carbon atoms [$C_{(4)}$, $C_{(5)}$, $C_{(10)}$] are coplanar, and conversion into a boat form is impossible, but substituents deviate only slightly from normal equatorial and axial conformations as in *cyclo*hexane. Ring B has the "half-chair" conformation as in *cyclo*hexene with four contiguous coplanar carbon atoms [$C_{(5)}$ $C_{(6)}$, $C_{(7)}$, $C_{(10)}$] (cf. Barton, Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21).

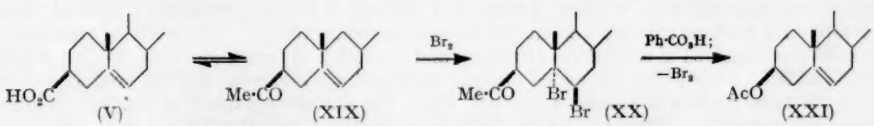
3β-CO_2R(equatorial)] by treatment with a solution from sodium and diethylene glycol or with sodium methoxide.



The foregoing configurational proofs involve the partial synthesis of an appropriately orientated steroid-3-acetic acid and its degradation to a steroid-3-carboxylic acid. We have therefore correlated cholest-5-ene-3β-carboxylic acid (V; R = H) with cholesterol, whose configuration is established (Shoppee, *J.*, 1948, 1032), by oxidation with perbenzoic acid. The conversion of steroid 20-ketones into 17-acetoxy-steroids by oxidation with persulphuric acid or by Caro's acid was first achieved by Marker *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 525, 650, 2543, 2621, 3003) and it was later observed that perbenzoic acid was also effective (Burckhardt and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 1434; Sarett, *J. Amer. Chem. Soc.*, 1947, **69**, 2899; Wieland and Miescher, *Helv. Chim. Acta*, 1949, **32**, 1768, 1922). The stereochemical course of these peroxidations was studied by Turner (*J. Amer. Chem. Soc.*, 1950, **72**, 878) and by Gallagher and Kritchevsky (*ibid.*, p. 882), who proved that configuration is preserved. The mechanism has been elucidated by Doering *et al.* (*ibid.*, 1950, **72**, 5515; 1953, **75**, 5595) and by Bunton, Lewis, and Llewellyn (*Chem. and Ind.*, 1954, 191) using isotopic oxygen, and shown to involve the pinacolic change :



The migrating steroid nucleus never leaves the system; thus it has been shown by Mislow and Brenner (*J. Amer. Chem. Soc.*, 1953, **75**, 2318) that optically active 3-phenylbutan-2-one is converted by treatment with perbenzoic acid into optically active 1-phenylethyl acetate with retention of configuration ($Ph\overset{*}{C}HMe\cdot CO\cdot CH_3 \longrightarrow Ph\overset{*}{C}HMe\cdot OAc$), which is consistent with the preservation of configuration quoted above and observed in other pinacolic migrations (Kenyon *et al.*, *J.*, 1939, 916; 1946, 25; Lane and Wallis, *J. Amer. Chem. Soc.*, 1941, **63**, 1674). The acid (V) was converted into the ketone (XIX) by successive



treatment with thionyl chloride and dimethylcadmium as described by Baker and Squire (*J. Amer. Chem. Soc.*, 1948, **70**, 1487), who proved that these compounds correspond in regard to configuration at $C_{(3)}$ by regenerating the acid from the ketone by King's method

(*ibid.*, 1944, **66**, 894, 1612). The ketone (XIX) was converted by treatment with bromine into the 5α : 6β-dibromide (XX), which by prolonged treatment with perbenzoic acid in chloroform at 0° and debromination with potassium iodide–acetone gave cholesteryl acetate (XXI). Marker's acid is therefore cholest-5-ene-3β-carboxylic acid.*

We have examined the Grignard carboxylation of *epi*cholesteryl bromide, but we defer discussion of this reaction and of the stereochemical course of the Grignard carboxylations of cholesteryl bromide and the epimeric cholestanyl bromides. We wish here, however, to draw attention to the anomalous optical rotatory power of cholest-5-ene-3β-carboxylic acid. The molecular rotations of the epimeric cholest-5-ene- and cholestane-carboxylic acids and cholesteryl- and cholestanyl-acetic acids and their methyl esters are given in the Table.

	Cholest-5-ene-carboxylic acids			Cholestane-carboxylic acids		
	3α	3β	$\Delta_{3\beta-3\alpha}$	3α	3β	$\Delta_{3\beta-3\alpha}$
Acid	−165°	−41°	+124°	+100°	+121°	+21°
Methyl ester	−171	−53	+118	+116	+128	+12
	Cholesterylacetic acids			Cholestanylacetic acids		
	3α	3β	$\Delta_{3\beta-3\alpha}$	3α	3β	$\Delta_{3\beta-3\alpha}$
Acid	−120°	−133°	−13°	+121°	+99°	−22°
Methyl ester	−128	−141	−13	+109	+86	−23

It will be seen that the carboxylic acids and esters break the rule that the difference $\Delta[M_D]_{\beta-\alpha}$ is a negative quantity for 3-substituted cholest-5-enes and cholestanes; the Δ value is especially large for the unsaturated cholest-5-ene-3-carboxylic acids and esters.

Experimental

Cholesteryl Bromide.—Cholesteryl bromide was prepared by a slight modification of the method of Bide, Henbest, Jones, Peevers, and Wilkinson (*J.*, 1948, 1786). Cholesterol (50 g.) was dissolved in chloroform (100 c.c.) and dimethylaniline (20 c.c.). The mixture was stirred under conditions to exclude moisture, and a solution of thionyl bromide (12 c.c.) in chloroform (40 c.c.) was added with ice-cooling during 15 min. Stirring was then continued at 20° for a further 0·5 hr. and the mixture poured into 95% ethanol (500 c.c.). After cooling for 1 hr. in cold water, the crystalline product was removed and the mother-liquors were diluted with water (150 c.c.) to give a further quantity of crystalline material. The crystalline product, recrystallised from acetone (300 c.c.), gave cholesteryl bromide (48 g., 85%) as plates, m. p. 97—98° (the previous workers reported a yield of 34 g., 60%, but their m. p. of 100—102° could not be observed even after repeated crystallisation from acetone).

3β-*Cholestanyl Bromide.*—Cholesteryl bromide (10 g.) in ether (100 c.c.) and acetic acid (20 c.c.) was shaken in hydrogen with platinum oxide (800 mg.) for 18 hr. The catalyst was filtered off and the acetic acid removed from the ether layer by alkaline washing. Drying and removal of solvent furnished 3β-cholestanyl bromide still containing some unsaturated material. The product was therefore dissolved in carbon tetrachloride (100 c.c.) and acetic anhydride (10 c.c.), sulphuric acid (1·4 c.c.) was added slowly, the mixture shaken for 15 min., and water added. After being washed to neutrality with sodium chloride solution and 2N-sodium carbonate, the solution was dried and evaporated. The product was passed through a column of aluminium oxide (100 g.) in pentane, the filtrate evaporated, and the residue crystallised from acetone, to furnish 3β-cholestanyl bromide, m. p. 114—115°, giving no colour with tetranitromethane–chloroform.

3α-*Cholestanyl Bromide.*—Cholestanol (18 g.) was dissolved in refluxing benzene (100 c.c.), and phosphorus tribromide (9 c.c.) added dropwise during 1 hr. After 1·5 hr., the solvents were removed in a vacuum and the residue poured into water. Extraction with ether, removal of a trace of insoluble material, washing, drying, and removal of solvent, furnished a product which was filtered in pentane through a column of aluminium oxide (100 g.). The crude 3α-cholestanyl bromide was dissolved in chloroform (100 c.c.), and a solution of perbenzoic acid (30 c.c.; 0·0266 g./c.c.) added. After 24 hr., the excess of perbenzoic acid was destroyed and the product worked up in the usual manner to furnish a product, which was chromatographed in pentane on aluminium oxide (100 g.). Pentane (1·1 l.) eluted 3α-cholestanyl bromide (7·9 g.), m. p. 103° (from acetone), giving no colour with tetranitromethane–chloroform.

* Since this paper was written, a similar conclusion has been reached by Corey and Sneen (*J. Amer. Chem. Soc.*, 1953, **75**, 6234) by a similar conversion of the acid (XI; R = H) into cholestanol.

Cholest-5-ene-3β-carboxylic Acid.—Cholesteryl bromide (100 g.), dissolved in ether (1 l.), was added during 3 hr. to a solution of methylmagnesium iodide, prepared from methyl iodide (40 c.c.), in ether (400 c.c.), and magnesium (36 g.). A further addition of methyl iodide (10 c.c.) was made after 12 hr. of a total reflux period of 40 hr. The mixture was then cooled and an excess of solid carbon dioxide added; after 1 hr., the complex was hydrolysed by addition of ice-cold 2N-sulphuric acid. The aqueous layer was removed and after being washed with water and dilute sodium thiosulphate solution the ethereal layer was filtered to remove the suspension of " bicholesteryl " and cholest-5-ene-3β-carboxylic acid (yield, 36·5 g.). After being dried, the ethereal filtrate was evaporated and the residue extracted with pentane to leave the insoluble cholest-5-ene-3β-carboxylic acid. The pentane-soluble material was dissolved in pentane and extracted with N-potassium hydroxide. Acidification and ether-extraction of the aqueous washings furnished a pentane-insoluble residue (700 mg.), m. p. 218—220°, identical with the main product. No trace of the pentane-soluble epimeric 3α-acid could be found. Most of the " bicholesteryl " was removed from the first crystalline fraction by warming with ether (1000 c.c.) removing the insoluble " bicholesteryl," and evaporating the filtrate to dryness. The total yield of acid was 48 g. All three fractions crystallised from ether–pentane as needles, m. p. 218—220°, $[\alpha]_D$ −10° (*c*, 1·0).

Methyl Cholest-5-ene-3β-carboxylate.—Crude cholest-5-ene-3β-carboxylic acid was esterified with ethereal diazomethane; the product was dissolved in acetone–methanol and filtered to remove " bicholesteryl." Fractional crystallisation from methanol gave methyl cholest-5-ene-3β-carboxylate as long needles, five consecutive fractions melting between 99° and 101°. A sample of the crude ester (1 g.) was chromatographed on a column of aluminium oxide (30 g.) prepared in pentane; elution with pentane (100 c.c.) gave five fractions, which after crystallisation from methanol had identical m. p. 100—101°, and gave no depression on admixture. Further elution of the column did not yield any material. Subsequently, the crude acid (25 g.) was dissolved in methanol (3 l.), and concentrated sulphuric acid (25 c.c.) was slowly added. After refluxing for 8 hr., the mixture was decanted from the contaminating " bicholesteryl," and the solution was concentrated. Cooling gave methyl cholest-5-ene-3β-carboxylate as long needles, which, recrystallised from methanol had m. p. 101°, $[\alpha]_D$ −11° (*c*, 1·4) (23 g.).

Cholestane-3β-carboxylic Acid.—(*a*) Cholest-5-ene-3β-carboxylic acid (200 mg.) in ether (10 c.c.) and acetic acid (10 c.c.) was shaken in hydrogen with platinum oxide (50 mg.). Hydrogenation was completed within 10 min. Removal of solvent and catalyst gave cholestane-3β-carboxylic acid, recrystallised from ether–pentane as needles, m. p. 206—208°, $[\alpha]_D$ +29° (*c*, 1·1). The methyl ester, prepared by using ethereal diazomethane and crystallised from methanol, had a double m. p. 54—56°/69°, $[\alpha]_D$ +27°.

(*b*) 3β-Cholestanyl bromide (5 g.) was added during 6 hr. to a solution of methylmagnesium iodide prepared from magnesium (1 g.), methyl iodide (0·3 c.c.), and ether (60 c.c.). Further methyl iodide (0·6 c.c.) was added with the 3β-cholestanyl bromide, and a further portion (0·6 c.c.) after 12 hr. After 20 hours' refluxing, solid carbon dioxide was added and after being kept for 1·5 hr. the complex was decomposed by ice-cold 2N-sulphuric acid. The ethereal solution was washed, the insoluble " bicholestanyl " removed, the solution dried and evaporated, and the product extracted with pentane to leave cholestane-3β-carboxylic acid as a solid which was esterified with diazomethane and chromatographed on a column of aluminium oxide (50 g.) prepared in pentane. Pentane (5 × 50 c.c.) eluted " bicholestanyl " (56 mg.), m. p. 298°, after separation of a little cholestane, m. p. and mixed m. p. 75—77°, by treatment with hot ethyl acetate–methanol; further elution with pentane (5 × 50 c.c.) and benzene–pentane (1 : 9; 4 × 50 c.c.) furnished a solid (total, 0·82 g.) which recrystallised from methanol; all the individual fractions melted at 68°, some exhibiting a double m. p. 52—54°/68°. No depression of m. p. was observed with methyl cholestane-3β-carboxylate obtained by the previous method.

(*c*) 3α-Cholestanyl bromide (5 g.) in ether (70 c.c.) was added during 5 hr. to a solution of methylmagnesium iodide prepared from magnesium (1·2 g.), methyl iodide (1·5 c.c.), and ether (50 c.c.). A further quantity of methyl iodide (0·6 c.c.) was added during the reflux period of 28 hr. Solid carbon dioxide was added and then, after 16 hr., the complex was decomposed with 2N-sulphuric acid, the product was extracted with ether, the suspended " bicholestanyl " was removed, and the ether extracts were washed, dried, and evaporated. The residue was extracted with pentane, and the pentane-insoluble material esterified with diazomethane, dissolved in acetone–methanol, and filtered to remove insoluble " bicholestanyl," m. p. ~298°. Fractional crystallisation from acetone–methanol afforded three crops of crystals: (1) needles, m. p. 69°; (2) plates, m. p. 68—70°; (3) plates, double m. p. 56°/68—70°, $[\alpha]_D$ +26° (*c*, 0·61), all consisting of methyl cholestane-3β-carboxylate. The mother-liquor material was chromato-

graphed on a column of aluminium oxide (6 g.) prepared in pentane. Benzene–pentane (1 : 4) eluted all the material, which crystallised from methanol, to give methyl cholestane-3β-carboxylate as needles, m. p. 69°.

(*d*) Cholestane-3α-carboxylic acid (Shoppee and Stephenson, *loc. cit.*) (27 mg.) was refluxed in diethylene glycol (4 c.c.) with potassium hydroxide (80 mg.) for 1 hr., the mixture cooled and poured into cold 2N-sulphuric acid, and the precipitate filtered off, washed, and dried. The product was dissolved in ether and decanted from a trace of amorphous material. Fractional crystallisation from ether–pentane furnished crystals (10 mg.), m. p. 203—207°, showing no depression when admixed with cholestane-3β-carboxylic acid. A further crop of crystals (10 mg.) melted over the range 160—195°.

(*e*) Methyl cholestane-3α-carboxylate (20 mg.) was heated at 180° for 3 hr. with N-sodium methoxide in methanol (4 c.c.). The usual working up afforded cholestane-3β-carboxylic acid which, crystallised from ether–pentane, had m. p. and mixed m. p. 206—208°. Methyl cholestane-3β-carboxylate (m. p. 54—56°; 16 mg.) was refluxed for 2 hr. with dry N-sodium methoxide (6 c.c.); the product consisted only of neutral material, and by recrystallisation from methanol gave unchanged starting material, m. p. and mixed m. p. 54—56°.

"*Bicholestan-3β-yl.*"—Formed from either of the cholestanyl bromides, this had m. p. and mixed m. p. 297—298°, $[\alpha]_D$ +42°, +38° [*c*, 0·09, 0·06, determined in a 4-dm. tube; Squire (*J. Amer. Chem. Soc.*, 1951, **73**, 2586) gives decomp. at 265—270°, m. p. >300°, $[\alpha]_D$ 0°]. The highest m. p. we observed was 305°.

2-(*Cholest-5-en-3α-yl*)-1 : 1-*diphenylethanol.*—To a solution of phenylmagnesium bromide, prepared from magnesium (1·05 g.), bromobenzene (4·6 c.c.), and ether (15 c.c.), was added a solution of methyl cholest-5-en-3α-ylacetate (1·15 g.) in ether (20 c.c.). After 3 hr. at 15°, the solution was poured into ice-cold ammonium chloride solution; the product was extracted with ether, washed, dried, and evaporated. The residual oil on being heated at 100°/0·03 mm. for 10 min., gave a sublimate (600 mg.), identified as diphenyl. The residue (1·3 g.) did not crystallise.

2-(*Cholest-5-en-3α-yl*)-1 : 1-*diphenylethylene.*—2-(Cholest-5-en-3α-yl)-1 : 1-diphenylethanol (1·3 g.), dissolved in benzene (50 c.c.) containing pyridine (4 c.c.), was treated with thionyl chloride (2 c.c.) at 0°. After 20 min., excess of thionyl chloride was destroyed by adding water, the product extracted with ether, and the solution, washed, dried, and evaporated. The residual oil was freed from coloured impurities by filtration in pentane through a column of aluminium oxide to furnish 2-(cholest-5-en-3α-yl)-1 : 1-diphenylethylene (870 mg.) as an oil which failed to crystallise.

Cholest-5-ene-3α-carboxylic Acid.—(*a*) Cholest-5-ene-3β-carboxylic acid (10·5 g.) was added to a solution from sodium (5 g.) in diethylene glycol (400 c.c.), the mixture refluxed for 3 hr., cooled, poured into water, acidified, and filtered, and the precipitate washed and dried. The powdered product was shaken with pentane (100 c.c.) and filtered; the pentane-soluble portion was crystallised from acetone (20 c.c.) to remove a quantity (~50 mg.) of cholest-5-ene-3β-carboxylic acid. The acetone solution was evaporated to dryness and the residue crystallised from 90% acetic acid, to yield cholest-5-ene-3α-carboxylic acid (420 mg.), m. p. 155°, $[\alpha]_D$ −40° (*c*, 1·2) [Found (after sublimation at 180°/0·01 mm.): C, 79·8; H, 10·9. Calc. for $C_{28}H_{46}O_2$: C, 81·1; H, 11·2%]. Although the acid gave poor analyses the *methyl ester*, prepared by ethereal diazomethane and crystallised from ether–methanol, had m. p. 112—114°, $[\alpha]_D$ −40° (*c*, 1·2) and was pure [Found (after sublimation at 140°/0·01 mm.): C, 81·3; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·2; H, 11·3%]. The ethyl ester, prepared by diazoethane, had m. p. 56—59° (from methanol); 9 g. of cholest-5-en-3β-yl-carboxylic acid were recovered.

(*b*) 2-(Cholest-5-en-3α-yl)-1 : 1-diphenylethylene (870 mg.) was dissolved in dioxan (50 c.c.) and acetic acid (100 c.c.). A solution of chromium trioxide (1 g.) in water (2 c.c.) was added and the solution kept at 25° for 14 hr. Excess of chromium trioxide was destroyed by adding methanol, the solvents were removed in a vacuum, 2N-sulphuric acid was added, and the product extracted with ether. Extraction of the ether layer with N-potassium hydroxide furnished, after acidification and ether-extraction, a solid soluble in pentane and acetone. Esterification with ethereal diazomethane furnished a sticky solid (150 mg.), chromatographed on a column of neutralised aluminium oxide (9 g.) prepared in pentane. Elution with benzene–pentane (2 : 3; 2 × 15 c.c.) furnished a solid (26 mg.), which crystallised from methanol as plates, m. p. 112°, and gave no depression on admixture with methyl cholest-5-ene-3α-carboxylate prepared by the previous method. Further elution gave only oils.

Cholest-5-ene-3β-carboxyamide.—Cholest-5-ene-3β-carboxylic acid (1·0 g.) was refluxed for 2 hr. in benzene (12 c.c.) with thionyl chloride (1 c.c.). The solvents were then removed under

reduced pressure, the acid chloride was dissolved in ether (15 c.c.), and a current of dry ammonia gas bubbled through for 15 min. Dilution with ether, washing, drying, and removal of solvent gave, after crystallisation from ether–pentane, cholest-5-ene-3β-carboxyamide, m. p. 227—229° (Baker and Squire, *J. Amer. Chem. Soc.*, 1948, **70**, 4134, give m. p. 227—228°, $[\alpha]_D$ −26°).

Cholestane-3β-carboxyamide.—Cholestane-3β-carboxylic acid (350 mg.) was refluxed in benzene (5 c.c.) with thionyl chloride (0·5 c.c.) for 2 hr.; removal of solvent, and treatment of the acid chloride dissolved in ether (5 c.c.) with dry ammonia, gave after further dilution with ether and the usual washing, drying, and removal of solvent, *cholestane-3β-carboxyamide* which, crystallised from ether–pentane, had m. p. 210—212°, $[\alpha]_D$ +26° (*c*, 1·0) (yield 310 mg.) [Found (after sublimation at 210/0·02 mm.): C, 80·6, H, 11·7. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9%].

Cholestane-3α-carboxyamide.—Cholestane-3α-carboxylic acid (300 mg.) was refluxed in benzene (5 c.c.) with thionyl chloride (0·5 c.c.) for 1·15 hr. After removal of solvents under reduced pressure, the acid chloride, dissolved in dry ether (5 c.c.), was treated with ammonia for 15 min., the product diluted with ether, washed, and dried, and the solvent removed, to furnish *cholestane-3α-carboxyamide* which, crystallised from ether–pentane, had m. p. 160—162°, $[\alpha]_D$ +22° (*c*, 0·8) (yield 250 mg.) [Found (after sublimation at 170°/0·02 mm.): C, 81·0; H, 12·1; N, 3·8. $C_{28}H_{49}ON$ requires C, 80·9; H, 11·9; N, 3·4%]. The mixture of this amide with the acid (m. p. 163°) from which it was derived melted at 170° and then resolidified to melt again at 206—210°.

Cholest-5-en-3β-yl Cyanide.—(*a*) Cholesteryl bromide (2 g.) was added to a solution of potassium cyanide (2 g.) in diethylene glycol (20 c.c.), and the mixture refluxed for 30 min. at 235°; some hydrogen cyanide was evolved. The mixture was cooled, diluted with water, and extracted with ether to yield, after the usual working up, an oil which was chromatographed on a column of aluminium oxide (50 g.) prepared in pentane. Elution with pentane (3 × 200 c.c.) furnished a solid (856 mg.) which, crystallised from acetone, had m. p. 70—73°, and gave an immediate red Rosenheim colour and no depression of m. p. on admixture with cholesta-3 : 5-diene. Further elution with pentane–benzene (3 : 7, 200 c.c.; 2 : 1, 200 c.c.) gave a solid (400 mg.) which crystallised from ether–methanol, to give *cholest-5-en-3β-yl cyanide* (75 mg.) as plates, m. p. 179—180°, $[\alpha]_D$ −16·5° (*c*, 1·7) [Found (after sublimation at 180°/0·02 mm.): C, 84·8; H, 11·5; N, 3·4. $C_{28}H_{45}N$ requires C, 85·0; H, 11·5; N, 3·5%]. Elution with benzene and then with ether gave only oils.

(*b*) *epi*Cholesteryl bromide (1 g.) with a solution of potassium cyanide (1 g.) in diethylene glycol (15 c.c.) was raised to 235° during 10 min.; refluxing was then continued for a further 15 min., the solution cooled, diluted with water, and extracted with ether, and the extract washed, dried, and evaporated. The product was chromatographed on aluminium oxide (25 g.). Pentane (2 × 75 c.c.) eluted a solid (586 mg.) which, crystallised from acetone, had m. p. 70—73° and consisted essentially of cholesta-3 : 5-diene. Elution with benzene (1 × 75 c.c.) furnished a sticky solid, which crystallised from ether–ethanol as plates (17·5 mg.), m. p. 150—175°. A further elution with benzene (1 × 75 c.c.) gave a solid which crystallised from ether–methanol to furnish cholest-5-en-3β-yl cyanide (3·5 mg.), m. p. and mixed m. p. with material obtained from cholesteryl bromide, 179—181°. Further elution with benzene and ether gave only oils.

The material, m. p. 150—175°, was rechromatographed on aluminium oxide (1·5 g.). Elution with pentane–benzene (17 : 3; 4 c.c.) gave a solid (8·2 mg.), which crystallised from ether–ethanol as plates, m. p. 135—160°. Further elution with pentane–benzene (3 : 1, 4 c.c.) furnished material (11·0 mg.), which crystallised from ether–ethanol as plates, m. p. 170—176°, mixed m. p. with cholest-5-en-3β-yl cyanide, 172—178°.

(*c*) Cholest-5-ene-3β-carboxyamide (140 mg.) was dissolved in toluene (5 c.c.) and treated with phosphorus oxychloride (0·5 c.c.) at 100° for 30 min. The solvents were removed under reduced pressure, the product was dissolved in ether, and the solution washed, dried, and evaporated. Crystallisation from ether–methanol furnished cholest-5-en-3β-yl cyanide, m. p. 178—180°, giving no depression of melting point with specimens prepared by methods (*a*) and (*b*).

3α-Cholestanyl Cyanide.—Cholestane-3α-carboxyamide (150 mg.) was treated as in (*c*) above, giving *3α-cholestanyl cyanide*, plates, m. p. 168°, $[\alpha]_D$ +21° (*c*, 0·8) [Found (after sublimation at 180°/0·02 mm.): C, 84·8; H, 12·1. $C_{28}H_{47}N$ requires C, 84·6; H, 11·9; N, 3·5%].

3β-Cholestanyl Cyanide.—Cholestane-3β-carboxyamide (120 mg.), similarly treated, gave *3β-cholestanyl cyanide*, m. p. 152°, $[\alpha]_D$ +27·5° (*c*, 1·5) [Found (after sublimation at 170°/0·02 mm.): C, 84·6; H, 11·9; N, 3·8%].

3α-Cholestanyl Cyanide (Equilibrium Mixture).—(*a*) 3α-Cholestanyl bromide (1 g.) was refluxed with potassium cyanide (1 g.) in diethylene glycol (15 c.c.) for 30 min.; the solution was cooled, diluted, and extracted with ether, and the ethereal extract washed, dried, and evaporated. Chromatography of the product on a column of aluminium oxide (25 g.) prepared in pentane

gave a solid (490 mg.) when pentane (2 × 75 c.c.) was used as eluant. Crystallisation from acetone gave needles, m. p. 66—67°, giving no depression on admixture with cholest-2-ene. Elution with benzene (3 × 75 c.c.) gave a solid (49 mg., 5%), which crystallised from methanol as needles, m. p. 124—126°, $[\alpha]_D$ +26·5° (*c*, 1·7), and consisted of a mixture of cholestan-3β- and 3α-yl cyanides [Found (after sublimation at 170°/0·02 mm.): C, 84·7; H, 12·2; N, 3·4%]. Further elution with benzene and ether gave only oils.

(*b*) 3β-Cholestanyl bromide (8·3 g.) was refluxed with potassium cyanide (10 g.) in diethylene glycol for 45 min. Working up in the usual way gave an oil which was introduced on to a column of aluminium oxide (220 g.), prepared in pentane. Elution with pentane furnished a solid, m. p. 66°, which crystallised from acetone as needles, m. p. 66—68°, identical with the cholest-2-ene isolated in the previous experiment. Elution with pentane–benzene (7 : 3, 2 × 800 c.c.; 3 : 2, 2 × 800 c.c.; 1 : 1, 800 c.c.) furnished a solid (total, 1·55 g., 21%), which crystallised from ether–ethanol to give 3αβ-cholestanyl cyanide, m. p. 125°, identical with that obtained in the previous preparation. Traces of crystalline material could, however, be observed in the melt until 150°, and this inhomogeneity was apparent in all fractions obtained by fractional crystallisation of the product from ether–ethanol. Further elution with ether gave only oils.

(*c*) 3α-Cholestanyl cyanide (12 mg.; m. p. 168°) was refluxed with potassium cyanide (15 mg.) in diethylene glycol (1·5 c.c.) for 1 hr. Dilution with water, followed by extraction of the product with ether, gave, after the usual working up, 3αβ-cholestanyl cyanide, which crystallised from ether–methanol to give a product of m. p. and mixed m. p. 124—126° with material prepared by methods (*a*) and (*b*).

(*d*) 3β-Cholestanyl cyanide (33 mg.; m. p. 152°) was refluxed in diethylene glycol with potassium cyanide (60 mg.) for 45 min. The usual working up gave a product which, crystallised from ether–methanol, had m. p. 126—128°, giving no depression of m. p. by admixture with cholestan-3αβ-yl cyanide prepared by methods (*a*), (*b*), and (*c*).

Synthetic mixtures of cholestan-3α- and -3β-yl cyanide gave the following melting points: 75% 3β-cholestanyl cyanide + 25% 3α-cyanide 128—147°; 50% 3β-cholestanyl cyanide + 50% 3α-cyanide 126°; 25% 3β-cholestanyl cyanide + 75% 3α-cyanide 160—168°. The equilibrium mixture described as 3αβ-cholestanyl cyanide therefore contains approx. 60% of the 3β-epimeride.

Cholestane-3β-carboxylic Acid.—Attempts to hydrolyse 3αβ-cholestanyl cyanide by refluxing methanolic potassium hydroxide or methanolic sulphuric acid furnished only starting material.

3αβ-Cholestanyl cyanide (150 mg.) was refluxed in diethylene glycol (12 c.c.) with potassium hydroxide (250 mg.) for 30 min. The usual working up gave a product which crystallised from ether–pentane as fine needles, m. p. 204—206°, showing no depression of m. p. by admixture with authentic cholestane-3β-carboxylic acid, m. p. 209—210°. A specimen of the methyl ester melted at 69°, both alone and by admixture with methyl cholestane-3β-carboxylate.

Cholest-5-ene-3β-carboxylic Acid.—Cholest-5-en-3β-yl cyanide (70 mg.) was refluxed in diethylene glycol (5 c.c.) with a solution of potassium hydroxide (80 mg.) in water (0·2 c.c.) for 1 hr., then diluted with water, acidified, and extracted with ether. The product, obtained by the usual working up, gave by trituration with pentane a crystalline solid (50 mg.), m. p. 217—222°, giving no depression by admixture with authentic cholest-5-ene-3β-carboxylic acid.

3β-*Acetylcholest-5-ene.*—A solution of methylmagnesium iodide, prepared from magnesium (2·75 g.), methyl iodide (4·4 c.c.), and ether (50 c.c.), was added slowly at 0° to a well-stirred suspension of cadmium chloride (11·7 g.) in ether (50 c.c.) in an atmosphere of nitrogen. The mixture was then refluxed for 30 min.

Cholest-5-ene-3β-carboxylic acid (12·9 g.) was refluxed in benzene (100 c.c.) with thionyl chloride (10 c.c.) for 3 hr. and kept at 15° for a further 12 hr.; the solvents were removed under reduced pressure. The acid chloride was added in ether (100 c.c.) to the dimethylcadmium in an atmosphere of nitrogen and refluxed with stirring for 1 hr.; 2N-hydrochloric acid was added, and the product isolated in the usual way. Filtration of a pentane solution through a column of aluminium oxide yielded, after removal of solvent and crystallisation from ether–methanol, 3β-acetylcholest-5-ene (9 g.), m. p. 103—104°, $[\alpha]_D$ −16·5° (*c*, 1·7) (Baker and Squire, *J. Amer. Chem. Soc.*, 1948, **70**, 1487, report m. p. 103—105°, $[\alpha]_D$ −11° (*c*, 3·4)].

3β-*Acetyl-5α* : 6β-*dibromocholestane.*—To a solution of 3β-acetylcholest-5-ene (1 g.) in chloroform (0·5 c.c.) and acetic acid (5 c.c.) was added a solution of bromine (0·42 g., 1·1 mol.) in acetic acid (3 c.c.). After 10 min., the solution was diluted with methanol, to yield the *dibromide*, which crystallised from ether–methanol as plates, m. p. 101°, $[\alpha]_D$ −55° (*c*, 1·8) (710 mg.) [Found (after drying at 20°/0·02 mm.): C, 61·0; H, 8·5; Br, 28·1. $C_{29}H_{48}OBr_2$ requires C, 60·8; H, 8·5; Br, 27·9%].

Cholesteryl Acetate.—3β-Acetyl-5α : 6β-dibromocholestane (100 mg.) was kept in a solution of perbenzoic acid (4 mol.) in chloroform (2 c.c.) for 4 weeks at 0°; the excess of perbenzoic acid was then destroyed, and the product worked up in the usual manner to yield an oil, which was debrominated by shaking with potassium iodide (300 mg.) in acetone (10 c.c.) for 10 min. at 15°. Dilution with water, extraction with ether, and washing with sodium thiosulphate solution, followed by drying and removal of solvent, gave an oil (61 mg.), which was introduced on to a column of aluminium oxide (2 g.) prepared in pentane. Pentane as eluant (3 × 6 c.c.) gave a solid (25 mg.), which after two crystallisations from acetone–methanol had m. p. 112°, and gave no depression by admixture with an authentic specimen of cholesteryl acetate, m. p. 113°. Elution with benzene–pentane combinations gave only oils.

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Triterpenoids. Part XVIII. The Constitutions of Phyllanthol and* cyclo*Artenol.*

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A method for the location of *cyclo*propane rings has been developed and applied to give a final solution for the constitutions of the *cyclo*propane triterpenoids phyllanthol and *cyclo*artenol. The method consists in opening the *cyclo*propane ring with, respectively, hydrogen chloride and deuterium chloride, and comparing the intensities of the C–H bending maxima in the infra-red absorption spectra of the two products. In this way the degree of substitution of the carbon atom to which the proton (deuteron) attaches itself may be determined. The direction of *cyclo*propane fission in steroid and terpenoid derivatives appears to be in accordance with the Markownikoff rule.

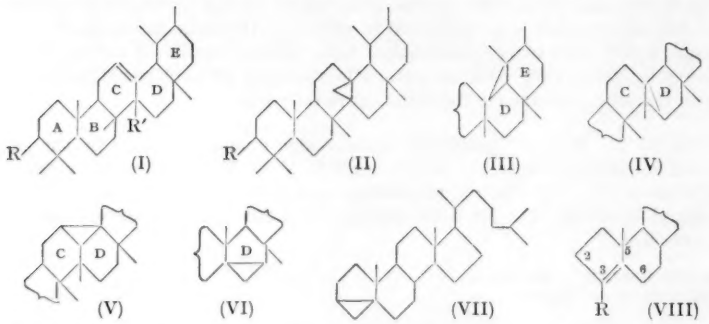
THE isolation of two *cyclo*propane triterpenoids, phyllanthol (Alberman and Kipping, *J.*, 1951, 2296; Barton and de Mayo, *J.*, 1953, 2178) and *cyclo*artenol (Barton, *J.*, 1951, 1444; Bentley, Henry, Irvine, and Spring, *J.*, 1953, 3673), has been reported. In both cases the structural problem has been reduced to the location of the *cyclo*propane ring. Thus the possible formulæ (Barton and de Mayo, *loc. cit.*) for phyllanthol, which affords α-amyrin (I; R = OH, R′ = Me) on acid-catalysed isomerisation, are (II—V; R = OH) and, conceivably, (VI; R = OH).

Now the opening of a *cyclo*propane ring by deuterium chloride (cf. Barton and de Mayo, *loc. cit.*) must afford one of the groupings $-CH_2D$, $>CHD$, or $>CD$. Methyl and methylene groups show infra-red absorption in the C–H bending region between 1300 and 1500 cm.$^{-1}$ (see R. N. Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; R. N. Jones, Cole, and Nolin, *ibid.*, p. 5662; Nolin and R. N. Jones, *ibid.*, 1953, **75**, 5626; Sheppard and Simpson, *Quart. Reviews*, 1953, **7**, 19) and therefore, if the infra-red spectra of *cyclo*propane compounds opened respectively with hydrogen chloride and deuterium chloride were compared, there would be observed a diminution in the intensity of the CH_3 peak at 1380 cm.$^{-1}$ or of the CH_2 peak near 1450 cm.$^{-1}$ depending on whether the grouping $-CH_2D$ or $>CHD$ were produced. If the grouping $>CD$ were formed there would be no change in the intensities of

* Part XVII, *J.*, 1954, 903.

the peaks at 1380 and 1450 cm.$^{-1}$. Thus a general method for the location of *cyclo*propane rings would become available.

In order to examine the feasibility of the procedure the fission of 3 : 5-*cyclo*cholestane (VII) to give (with hydrogen chloride) 3-methyl-A-norcholest-3(5)-ene (VIII; R = Me)



(Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582; Shoppee and Summers, *J.*, 1952, 2528) and (with deuterium chloride) the 3-deuteromethyl analogue (VIII; R = CH_2D) was investigated. As shown by the data summarised in the Table the reduction in intensity

Compound	Infra-red frequencies (cm.$^{-1}$) and, in parentheses, apparent molecular extinction coefficients: CH_2 ("aliphatic")	CH_2 ("ring")	CH_3 (*gem*)	CH_3	CH_3 (*gem*)	No. of CH_3 groups contributing to 1380 cm.$^{-1}$ max.	Intensity per CH_3 at 1380 cm.$^{-1}$ or equiv.
3-Methyl-A-norcholest-3(5)-ene (VIII; R = CH_3)	1470 (125)	1446 (108)	—	1380 (100)	1368 (100)	5	20
3-Deuteromethyl-A-norcholest-3(5)-ene (VIII; R = CH_2D)	1470 (117)	1446 (88)	—	1380 (82)	1368 (92)	4	20
α-Amyrene (I; R = H; R′ = CH_3)	—	1460 (152)	1386 (104)	1380 (138)	1370 (73)	6	23
27-Deutero-α-amyrene (I; R = H, R′ = CH_2D)	—	1460 (152)	1388 (108)	1382 (117)	1370 (69)	5	23
Lanost-9(11)-ene (IX; R = H, R′ = CH_3)	1466 (159)	1448 (91)	1386 (96)	1372 (161)	1364 (122)	5	32
19-Deuterolanostenes (IX; R = H, R′ = CH_2D; 7 : 8- and 8 : 9-ene isomers)	1466 (159)	1448 (93)	1386 (93)	1372 (129)	1364 (123)	4	32
Lanostane (XVI; R = CH_3)	1468 (167)	1450 (105)	— —	1386 (138)	1368 (112)	6	23
19-Deuterolanostane (XVI; R = CH_2D)	1468 (167)	1450 (107)	— —	1386 (120)	1368 (112)	5	24
3 : 5-*cyclo*Cholestane (VII)	1470 (138)	1446 (91)	— —	1380 (90)	1368 (70)	4	22
Phyllanthane (II; R = H)	—	1454 (148)	1386 (84)	1382 (120)	1368 (68)	5	24
*cyclo*Artane (X; R = H)	1468 (153)	1453 (123)	1380 (123)	1375 (116)	1364 (110)	4	29

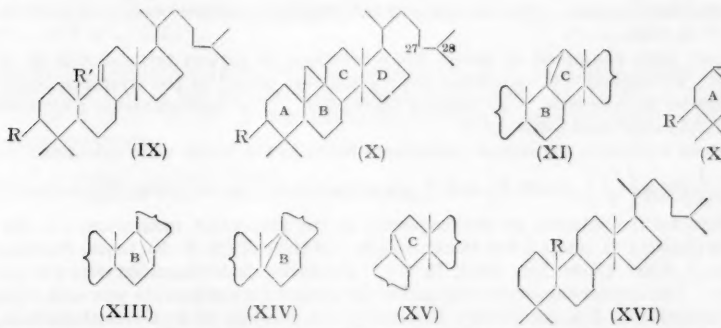
of the 1380 cm.$^{-1}$ band in the deutero-derivative was proportional to the change in the number of methyl groups contributing to this maximum.* Some reduction in the strength of the ring-methylene peak near 1450 cm.$^{-1}$ was also produced. This must be due to the

* The intensity values summarised in the Table are reported in apparent molecular extinction coefficients calculated as defined in the Experimental section. The corresponding data given in a previous Part of this series (Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571; see also *idem*, *Chem. and Ind.*, 1952, 426) were expressed in a purely arbitrary manner. Since, both in these papers and in the present article, relative values only are concerned, the form in which the intensity data are presented is of no significance.

(not unexpected) further deuteration (at $C_{(6)}$ and possibly at $C_{(2)}$) of (VIII; R = CH_2D) after the fission of the *cyclo*propane ring.

*cyclo*Propane fission of phyllanthane with deuterium chloride produced a deuteromethyl group, as shown by the infra-red results summarised in the Table. Since only (II; R = H) could afford such a grouping the constitution of phyllanthol must be (II; R = OH). This conclusion is confirmed by the intensity data for phyllanthane itself (see Table), which clearly has one less methyl group than α-amyrene (cf. the similar data for 3 : 5-*cyclo*cholestane also summarised in the Table).

*cyclo*Artanol, derived from *cyclo*artenol by saturation of the *iso*propylidene group in the side chain, affords a mixture of lanost-7-, -8-, and, mainly, -9(11)-enol (Bentley *et al.*, *loc. cit.*) on acid-catalysed isomerisation. The possible formulæ for *cyclo*artanol are (see Bentley *et al.*, *loc. cit.*) (X—XV; R = OH). Of these only (X; R = OH) would afford a deuteromethyl group based on a lanostane carbon skeleton on *cyclo*propane fission with deuterium chloride. That such a grouping was indeed produced was shown, first, by comparing the spectrum of the mixture of olefins [main component (IX; R = H, R′ = CH_2D)] formed by treatment of *cyclo*artane with deuterium chloride with that of lanost-9(11)-ene (IX; R = H, R′ = CH_3) (see Table). This conclusion was confirmed by consideration of the intensity of absorption at 1380 cm.$^{-1}$ of *cyclo*artane relative to that of lanost-9(11)-ene (IX; R = H, R′ = CH_3) and, more securely, in the following way. *cyclo*Artanyl acetate was converted by deuterium chloride into a mixture of 7-, 8-, and 9(11)-olefins. Catalytic hydrogenation of the 9(11)-ethylenic linkage (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893) gave a mixture of deuterated lanostanyl acetate and (unhydrogenatable) lanost-7- and -8-enyl acetate. Treatment with peracetic acid and chromatography afforded pure deuterated lanostanyl acetate which, by hydrolysis, oxidation, and Wolff–Kishner reduction, gave deuterated lanostane (XVI; R = CH_2D). The infra-red spectrum of the latter compound, compared with that of lanostane (XVI; R = CH_3) (see Table), revealed beyond question the presence of a deuteromethyl group. The formula of *cyclo*artenol is thus [X; R = OH and with an ethylenic linkage at position 27(28)].



(IX) (X) (XI) (XII)

(XIII) (XIV) (XV) (XVI)

The same conclusion as to the formula of *cyclo*artenol has also been reached independently by Henry and Spring (*Chem. and Ind.*, 1954, 220) on the basis of exclusion evidence. We cordially thank Professor F. S. Spring, F.R.S., for his kindness in sending us a copy of his preliminary communication before its publication.

The constitutions (II; R =OH) and [X; R = OH; double bond at position 27(28)] for phyllanthol and *cyclo*artenol respectively are in agreement with Cole's observations *ibid.*, 1953, 946; also personal communication) that both compounds have an infra-red peak at 3042—3052 cm.$^{-1}$ which may be regarded as characteristic of the C–H stretching frequency of a methylene group within a *cyclo*propane ring.

With simple *cyclo*propane compounds acid-catalysed fission proceeds in accordance with the Markownikoff rule (see Raphael in Robinson and Rodd's " The Chemistry of Carbon Compounds," Elsevier Publ. Corpn., Amsterdam, 1953, Vol. IIA, p. 26). The question of the applicability of this concept to complex polycyclic sustems of the type discussed in the

present paper is clearly of interest. The acid-catalysed isomerisations of 3 : 5-*cyclo*cholestane (VII), phyllanthol, and *cyclo*artanol are all in agreement with the rule. Of the other formulæ for phyllanthol, including those disproved by Barton and de Mayo (*loc. cit.*), only (III and IV; R = OH) might conceivably isomerise to α-amyrin with Markownikoff fission. Of the various possible formulæ for *cyclo*artanol (XII—XIV; R = OH), as well as the correct structure (X; R = OH), might all afford the observed product on Markownikoff fission.

The assignment of infra-red absorption frequencies to the *gem*-dimethyl groupings of the compounds listed in the Table requires comment. These frequencies often appear as side maxima or shoulders on the main 1380 cm.$^{-1}$ band. The intensities reported for these maxima are therefore misleading in that there is a substantial contribution from ordinary methyl groups. The *gem*-dimethyl group in the side chain of 3 : 5-*cyclo*cholestane (VII) and its derivatives (VIII; R = CH_3 and CH_2D) shows one methyl group absorbing at 1368 cm.$^{-1}$ and the other contributing to the main peak at 1380 cm.$^{-1}$. α-Amyrene (I; R = H, R′ = CH_3) and its deutero-derivatives showed *gem*-dimethyl peaks at 1386 cm.$^{-1}$ as well as at 1370 cm.$^{-1}$. This resolution of the *gem*-dimethyl peaks was also noted in lanost-9(11)-ene (IX; R = H, R′ = CH_3) and its deuterated derivatives, but not in lanostane (XVI; R = CH_3) and 19-deuterolanostane (XVI; R = CH_2D). In the last two compounds two methyl groups of the two *gem*-dimethyl groupings must be contributing to the 1368 cm.$^{-1}$ peak whilst the other two methyl groups are not separated but contribute to a 1368 cm.$^{-1}$ maximum which represents also all the other methyl groups.

Experimental

For general experimental details see Part VII (*J.*, 1952, 2339). Rotations were determined in chloroform solution. The deuterium oxide used was 99·65—99·74% pure (Norsk Hydro).

Infra-red Spectroscopy.—The spectroscopic measurements were made with a Perkin–Elmer Model 21 double-beam spectrophotometer. Although an instrument fitted with a calcium fluoride prism is to be preferred for quantitative measurements in the C–H bending region (see R. N. Jones and Cole, *loc. cit.*), satisfactory resolution was achieved in the present investigation with a sodium chloride prism. The accuracy of the frequency measurements for sharp maxima was about ±3 at 1500 cm.$^{-1}$.

The samples were examined as about 0·05M-solutions in carbon tetrachloride in 0·8-mm. rock-salt cells; a matched cell containing the solvent was placed in the reference beam of the spectrophotometer to compensate for solvent absorption. The measurements were conducted over the spectral range 4000—650 cm.$^{-1}$.

The apparent molecular extinction coefficients listed in the Table were calculated from the relation $\varepsilon_a = \frac{1}{cl} \log_{10} \left(\frac{T_0}{T} \right)$, where T_0 and T are respectively the radiation (%) transmitted by the solvent and by the solution at the frequency of the absorption maximum, c is the solute concentration (moles l.$^{-1}$), and l is the thickness (cm.) of the cell (cf. R. N. Jones, Ramsay, Keir, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 80). Duplicate determinations were run on nearly every sample. The reproducibility of the molecular extinction coefficients was well within 5%.

3-Methyl-A-norcholest-3(5)-ene (VIII; R = CH_3).—A solution of 3 : 5-*cyclo*cholestane, m. p. 79—80°, $[\alpha]_D$ +75° (*c*, 1·42) (Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582) (109 mg.), in alcohol-free chloroform (3 ml.) to which 4 drops of water had been added, was saturated with hydrogen chloride and left at room temperature for 1 day. The product (102 mg.) was chromatographed over alumina. Elution with light petroleum (b. p. 40—60°) and crystallisation from chloroform–methanol gave 3-methyl-A-norcholest-3(5)-ene, m. p. 64—64·5°, $[\alpha]_D$ +53° (*c*, 1·99) (cf. Schmid and Kägi, *loc. cit.*; Shoppee and Summers, *J.*, 1952, 2528). The deuterium analogue (VIII; R = CH_2D), of the same m. p. and rotation {$[\alpha]_D$ +54° (*c*, 2·31)}, was prepared according to the analogous procedure of Barton and de Mayo (*loc. cit.*).

α-Amyrene and Derivatives.—α-Amyrene, kindly prepared by Mr. K. H. Overton, had m. p. 117—118°, $[\alpha]_D$ +93° (*c*, 2·08). Phyllanthane, m. p. 173—174°, $[\alpha]_D$ +43° (*c*, 1·91), was prepared from phyllanthol according to Barton and de Mayo's directions (*loc. cit.*). Fission of the *cyclo*propane ring of this hydrocarbon with deuterium chloride according to Barton and de Mayo's directions (*loc. cit.*) gave 27-deutero-α-amyrene (I; R = H, R′ = CH_2D), m. p. 118—119°, $[\alpha]_D$ +89° (*c*, 1·65).

Lanostan-11-one.—This was prepared by an alternative method to that of McGhie, Pradhan, and Cavalla (*J.*, 1952, 3176). Potassium (300 mg.) in dry *tert.*-butanol (16 ml.) was heated with lanostane-3 : 7 : 11-trione (500 mg.) and anhydrous hydrazine (3 ml.) at 165° for 12 hr. The products from three such experiments (1·25 g. of trione used in all) were combined and chromatographed over alumina. Elution with light petroleum (b. p. 40—60°)–benzene(19 : 1) gave lanostan-11-one (276 mg., 22%). Recrystallised from chloroform–methanol this had m. p. 95—95·5°, $[\alpha]_D$ +59° (*c*, 2·04).

Lanostan-11β-ol.—A solution of lanostan-11-one (202 mg.) in sodium-dried ether (5 ml.) was added to a refluxing solution of lithium aluminium hydride (450 mg.) in the same solvent (10 ml.). Crystallisation of the product from chloroform–methanol afforded *lanostan-11β-ol*, m. p. 132—133°, $[\alpha]_D$ +52° (*c*, 2·45) (Found : C, 83·4; H, 12·4. $C_{30}H_{54}O$ requires C, 83·65; H, 12·65%). The alcohol (208 mg.) in anhydrous pyridine (10 ml.) and redistilled phosphorus oxychloride (1 ml.) with 1 drop of water was heated for 1 hr. on the steam-bath. Chromatography of the product over alumina, elution with light petroleum (b. p. 40—60°), and crystallisation from chlorofrom–methanol gave *lanost-9(11)-ene* (54 mg.), m. p. 86—87°, $[\alpha]_D$ +79° (*c*, 3·07) (Found : C, 87·6; H, 12·55. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%).

Other Derivatives of Lanostane.—*cyclo*Artane, m. p. 86—87°, $[\alpha]_D$ +54° (*c*, 2·23), was prepared according to Barton (*J.*, 1951, 1444). Treatment of *cyclo*artane (95 mg.) with deuterium chloride according to Barton and de Mayo's procedure (*loc. cit.*) gave a mixture of 19-deuterolanostenes (see Bentley, Henry, Irvine, and Spring, *loc. cit.*), m. p. 66—70°.

Similar treatment of *cyclo*artanyl acetate (377 mg.) (Barton, *loc. cit.*) gave a comparable mixture of isomers, m. p. 133—145° (cf. Bentley *et al.*, *loc. cit.*). This was hydrogenated in "AnalaR" acetic acid (50 ml.) over platinum oxide (200 mg.) at 80° until the $\varepsilon_{max.}$ at 203 mμ had decreased to 1200 [saturation of all 9(11)-olefinic material]. The product (354 mg.) in "AnalaR" acetic acid (25 ml.) and chloroform (5 ml.) was treated with 40% peracetic acid (2·5 ml.) and left overnight. Chromatography over alumina, elution with light petroleum (b. p. 40—60°)–benzene (3 : 1), and crystallisation from chloroform–methanol gave 19-deuterolanostanyl acetate, m. p. 147—151°, $[\alpha]_D$ +39° (*c*, 1·91). Hydrolysis, oxidation with chromic acid, and Wolff–Kishner reduction by standard procedures furnished 19-deuterolanostane, m. p. 97—98·5°, (from chloroform–methanol), $[\alpha]_D$ +33° (*c*, 1·84), which was saturated to tetranitromethane. An authentic specimen of lanostane, m. p. 97—98·5°, $[\alpha]_D$ +33° (*c*, 1·63), was prepared by Wolff–Kishner reduction of lanostan-3-one (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893).

We thank the Colonial Products Research Council (Dr. R. A. E. Galley) for kindly arranging for a further collection of the root bark of *Phyllanthus engleri*, Pax, by Mr. P. J. Greenaway (Kenya). One of us (E. W. W.) is indebted to the National Research Council of the U.S. for a Postdoctorate Fellowship.

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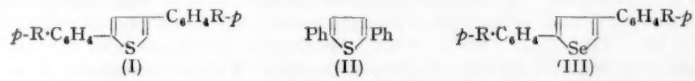
Thiophen Derivatives of Biological Interest. Part VII. The Synthesis of 2 : 4-Diarylthiophens and 2 : 4-Diarylselenophens from Anils of Alkyl Aryl Ketones.*

By P. Demerseman, Ng. Ph. Buu-Hoï, R. Royer, and Andrée Cheutin.

[Reprint Order No. 5276.]

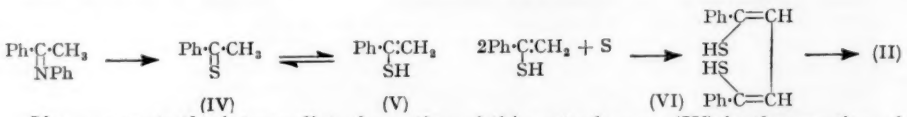
The Bogert synthesis of 2 : 4-diaryl-thiophens and -selenophens by the reaction of sulphur or selenium with the anils of alkyl aryl ketones has been investigated, and, in the case of sulphur, the formation of 2 : 5-diaryl-thiophens detected both spectroscopically and chemically. A mechanism is proposed to account for the two courses of the Bogert reaction and for the difference in behaviour between sulphur and selenium.

In connexion with another research, the preparation of 2 : 4-diphenylthiophen and its homologues was investigated. The most convenient recorded method was apparently that of Bogert and Herrera (*J. Amer. Chem. Soc.*, 1923, **45**, 238), based on the reaction of sulphur with acetophenone anil at 220—240°, which is reported to give pure 2 : 4-diphenylthiophen, to the exclusion of the 2 : 5-isomer. Repetition of this reaction gave, however, after repeated recrystallisation, a sample of 2 : 4-diphenylthiophen, m. p. 126°, which had an ultra-violet absorption spectrum differing from those of 1 : 3-diphenylbenzene and 2 : 4-diphenylselenophen (Fig. 1) in the presence of an additional band in the 3000—3200 Å



(I) (II) (III)

region. The fact that 2 : 5-diphenylthiophen (II) showed an absorption band in that very region (Fig. 2) suggested that Bogert and Herrera's 2 : 4-diphenylthiophen (I; R = H) contained an appreciable amount of the 2 : 5-isomer which could not be removed by crystallisation. This was proved by treating the impure 2 : 4-diphenylthiophen with an excess of *N*-methylformanilide and phosphorus oxychloride, 2 : 4-diphenylthiophen being readily converted into 3 : 5-diphenyl-2-thenaldehyde, whereas about 10% of 2 : 5-diphenylthiophen was recovered in the forerun on vacuum-distillation. A similar observation was made concerning the reaction of sulphur on *p*-methylacetophenone anil, the resulting 2 : 4-di-*p*-tolylthiophen (I; R = Me) containing some of its 2 : 5-isomer.



(IV) (V) (VI)

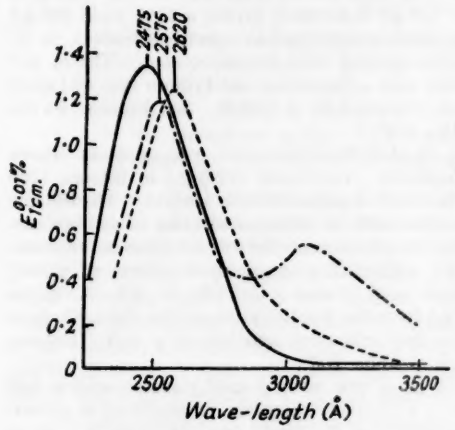
If one accepts the intermediate formation of thioacetophenone (IV) in the reaction of acetophenone anil with sulphur, the mechanism of the side reaction leading to 2 : 5-diphenylthiophen can be postulated as a sulphur dehydrogenation of two molecules of thioacetophenone in its thioenolic form (V). The intermediate bisthiophenacyl (VI) in its thioenolic form would then lose one molecule of hydrogen sulphide to yield 2 : 5-diphenylthiophen. This reaction mechanism resembles the Baumann–Fromm synthesis of 2 : 5-diphenylthiophen from cinnamic acid or styrene and sulphur (*Ber.*, 1895, **28**, 890). Further it should be noted that in the Willgerodt reaction between acetophenone and ammonium sulphide a mixture of 2 : 4- and 2 : 5-diphenylthiophen is formed (Willgerodt *et al.*, *J. pr. Chem.*, 1909, **80**, 192; 1910, **81**, 74, 382).

By contrast, reaction of acetophenone anil with selenium gave pure 2 : 4-diphenylselenophen (III; R = H); so did those with the anils of *p*-methylacetophenone and *p*-methoxyacetophenone; the absorption spectra of 2 : 4-diphenyl-, 2 : 4-di-*p*-tolyl- (III;

* Part VI, *J.*, 1954, 1975.

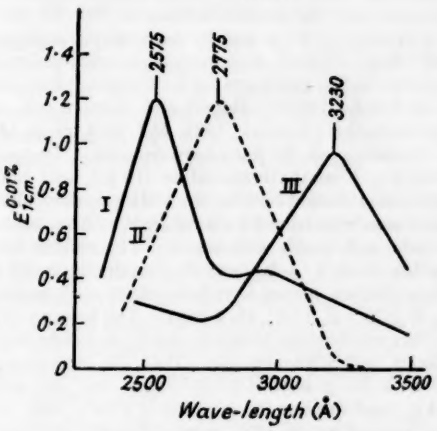
R = Me), and 2 : 4-di-*p*-methoxyphenyl-selenophen (III; R = OMe), recorded in Fig. 3, showed no abnormality. This difference in behaviour between sulphur and selenium could be ascribed to the smaller dehydrogenating power of the latter, and, in fact, no selen-

FIG. 1.



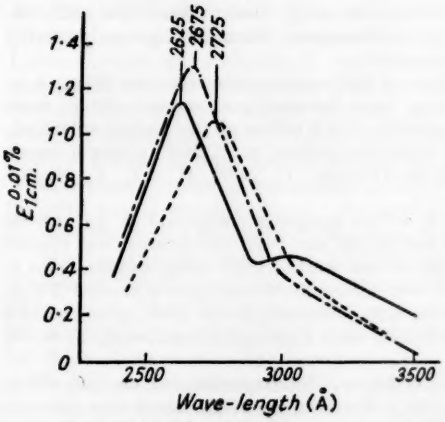
——— 1 : 3-*Diphenylbenzene.*
— · — · — *Impure* 2 : 4-*diphenylthiophen.*
- - - - - - - 2 : 4-*Diphenylselenophen.*

FIG. 2.



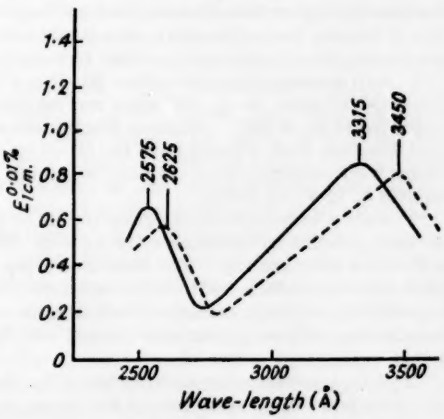
I, *Purified* 2 : 4-*diphenylthiophen.*
II, 1 : 4-*Diphenylbenzene.*
III, 2 : 5-*Diphenylthiophen.*

FIG. 3.



——— 2 : 4-*Di*-p-*tolylthiophen.*
— · — · — 2 : 4-*Di*-p-*tolylselenophen.*
- - - - - - - 2 : 4-*Di*-p-*methoxyphenylselenophen.*

FIG. 4.



——— 3 : 5-*Diphenyl-2-thenaldehyde.*
- - - - - - - 3 : 5-*Diphenyl-2-formylselenophen.*

ium-containing compound could be obtained when cinnamic acid or styrene was heated with selenium. An even more pronounced lack of reactivity was displayed by tellurium, which gave no trace of 2 : 4-diphenyltellurophen from acetophenone anil. The close similarity between 2 : 4-diphenylthiophen and 2 : 4-diphenylselenophen was further shown in the analogy of the ultra-violet absorption spectra of 3 : 5-diphenyl-2-thenaldehyde and 3 : 5-diphenyl-2-formylselenophen (Fig. 4), a bathochromic effect being observed in passing from the thiophen to the selenophen series.

Experimental

Reaction of Sulphur with Acetophenone Anil.—Acetophenone anil [best prepared by the method used by Hansch *et al.* (*J. Amer. Chem. Soc.*, 1951, **73**, 704) for the preparation of acetothienone anil] (60 g.) and sulphur (20 g.) were heated at 185—190° for 13 hr. in a distillation apparatus, with removal of the aniline formed. The dark brown mass was fractionated in a vacuum, and the portion boiling at 265°/35 mm. (22 g.) redistilled, giving a 51% yield (20 g.) of a mixture of 2 : 4- and 2 : 5-diphenylthiophen, which crystallised as colourless leaflets, m. p. 126°, from ethanol, and gave a greenish-yellow halochromy with sulphuric acid. The m. p.s reported in the literature for 2 : 4-diphenylthiophen vary : Baumann and Fromm (*loc. cit.*) gave m. p. 119·5—120·5°; Bogert and Herrera (*loc. cit.*) reported m. p. 122·5°; and Fromm, Fantl, and Leibsohn (*Annalen*, 1927, **457**, 267), m. p. 119—124°.

Isolation of 2 : 5-diphenylthiophen. Impure 2 : 4-diphenylthiophen prepared as above (23·5 g.), *N*-methylformanilide (19 g.), and phosphorus oxychloride (22·5 g.) in toluene (100 c.c.) were refluxed for 5 hr. and, after cooling, shaken with aqueous sodium acetate. The toluene layer was washed with dilute hydrochloric acid, then with an aqueous solution of sodium carbonate, and finally with water. The residue from evaporation of the solvent gave on vacuum-fractionation 3 : 5-diphenyl-2-thenaldehyde (22 g.), crystallising as colourless prisms, m. p. 94°, from ethanol, giving a yellow colour with sulphuric acid (Found : C, 77·6; H, 4·6. Calc. for $C_{17}H_{12}OS$: C, 77·3; H, 4·5%). The forerun (2 g.) from the fractionation of this aldehyde gave on recrystallisation from ethanol 2 : 5-diphenylthiophen (colourless needles), m. p. 156°; Bohme, Pfeifer, and Schneider (*Ber.*, 1942, **75**, 900) gave m. p. 155—156°.

2 : 4-*Di*-p-*tolylthiophen.*—This was prepared as above with *p*-methylacetophenone anil (64 g.) and sulphur (20 g.), to give a 34% yield of 2 : 4-di-*p*-tolylthiophen, crystallising as colourless prisms, m. p. 145°, from ethanol; on formylation of the crude product, some 2 : 5-di-*p*-tolylthiophen, m. p. 171° (Willgerodt and Hambrecht, *loc. cit.*), was isolated from the forerun.

2 : 4-*Di*-p-*tolylselenophen.*—This was prepared by heating 4-methylacetophenone anil (64 g.; b. p. 200—205°/15 mm.) and selenium (48 g.) for 18 hr. at 185°; distillation (b. p. 220—225°/0·5 mm.) and recrystallisation from ethanol gave colourless leaflets (18 g.), m. p. 140°, giving a blood-red colour with sulphuric acid. Although the 40% yield recorded for this preparation was considerably higher than that reported by Bogert and Andersen (*J. Amer. Chem. Soc.*, 1926, **48**, 223), it was far less satisfactory than for 2 : 4-diphenylselenophen, the methyl groups probably undergoing dehydrogenation to afford resinous by-products.

2 : 4-*Di*-p-*methoxyphenylthiophen* (I; R = OMe).—4-Methoxyacetophenone anil (69 g.; b. p. 210—215°/17 mm., m. p. 90° after recrystallisation from benzene) and sulphur (20 g.) were heated for 13 hr. at 180°. Vacuum-fractionation yielded a thick yellow oil (5 g.) which solidified; crystallisation from ethanol gave the *thiophen* as colourless prisms, m. p. 205°, giving a brown colour with sulphuric acid, rapidly becoming green (Found : C, 72·6; H, 5·1. $C_{18}H_{16}O_2S$ requires C, 72·9; H, 5·4%).

2 : 4-*Di*-p-*hydroxyphenylthiophen* (I; R = OH).—The foregoing compound (4 g.) and redistilled pyridine hydrochloride (10 g.) were refluxed for 20 min., and the product was treated with water after cooling. The dark brown precipitate was washed with water and dissolved in dilute aqueous sodium hydroxide; reprecipitation with hydrochloric acid gave a *product* (2·5 g.) crystallising as shiny, colourless leaflets from acetic acid (charcoal), m. p. 243°, giving a sepia halochromy with sulphuric acid (Found : C, 71·7; H, 4·5. $C_{16}H_{12}O_2S$ requires C, 71·6; H, 4·4%).

2 : 4-*Di*-p-*methoxyphenylselenophen* (III; R = OMe).—4-Methoxyacetophenone anil (69 g.) and selenium (48 g.) were heated for 18 hr. at 185°. Working up in the usual way gave the *selenophen* (45%), a viscous oil, b. p. 260—265°/0·5 mm., which solidified. Recrystallisation from ethanol–benzene gave colourless, sublimable needles, m. p. 214°, giving a red halochromy with sulphuric acid (Found : C, 62·9; H, 4·7. $C_{18}H_{16}O_2Se$ requires C, 62·9; H, 4·6%).

Ultra-violet Absorption Spectra.—A Beckman spectrophotometer was used, and measurements were made on solutions in pure ethanol, at a concentration of 10^{-5} g./c.c.

We thank Miss P. F. Boshell, M.A., for assistance.

The Radium Institute, University of Paris. [*Received, April 2nd*, 1954.]

Cytidine Nucleotides. Part I. Isolation from Lactobacillus arabinosus.

By J. Baddiley and A. P. Mathias.

[Reprint Order No. 5233.]

Dried cells of *Lactobacillus arabinosus* have been shown to contain cytidine-5′ phosphate. Young, rapidly killed, organisms do not contain this nucleotide, but contain two new cytidine derivatives which are derivatives of cytidine-5′ phosphate containing unidentified residues attached to the phosphate group. Other nucleotides from this organism have been separated by ion-exchange chromatography and many have been identified.

It was shown by Pierpoint and Hughes (*Biochem. J.*, 1954, **56**, 130) that *Lactobacillus arabinosus* 17—5, when grown in the absence of cystine, metabolises pantothenic acid but does not convert it into coenzyme A. The metabolic product has now been identified as pantothenic acid-4′ phosphate (Baddiley, Hughes, Mathias, and Pierpoint, *ibid.*, 1954, **56**, xxii). During this work it was noticed that considerable amounts of other phosphates with high absorption in ultra-violet light were present in extracts of cystine-deficient cells. A preliminary examination of aqueous extracts of this organism by chromatography and electrophoresis on paper suggested that these substances were nucleotides. A more detailed study of the nucleotides in *L. arabinosus* was therefore undertaken.

Aqueous extracts of the dried cystine-deficient organisms (kindly supplied by Dr. D. E. Hughes) were treated with barium acetate. After removal of insoluble barium salts the solution was examined by paper chromatography. Spots were observed which corresponded in position to the 5′-phosphates of adenosine, uridine, and cytidine. The presence of adenosine-5′ phosphate was not unexpected, since it would probably arise as a precursor or decomposition product of adenosine di- and tri-phosphate and the several known coenzymes which are derived from this nucleotide. Similarly, uridine-5′ phosphate might be expected as a precursor or decomposition product of uridine-diphosphate-glucose (Caputto, Leloir, Cardini, and Paladini, *J. Biol. Chem.*, 1950, **184**, 333), uridine-diphosphate-*N*-acetylglucosamine (Cabib, Leloir, and Cardini, *ibid.*, 1953, **203**, 1055), the recently isolated uridine triphosphate (Lipton, Morell, Frieden, and Bock, *J. Amer. Chem. Soc.*, 1953, **75**, 5449; Munch-Petersen, Kalckar, Cutolo, and Smith, *Nature*, 1953, **172**, 1036), or of other less-defined uridine pyrophosphate derivatives known to occur in living cells. On the other hand neither cytidine-5′ phosphate nor any derivative of this nucleotide has been isolated hitherto from a natural source. A possible exception is ribonucleic acid, in which cytidine residues are joined to neighbouring nucleosides through 3′ : 5′-phosphate linkages.

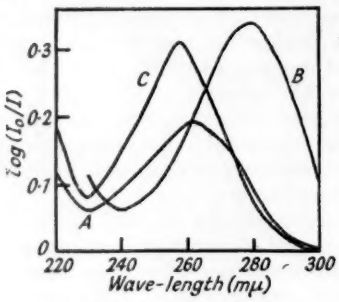
It was necessary then to establish beyond doubt that the new nucleotide was cytidine-5′ phosphate. Individual bands of the nucleotides were eluted from the paper and their ultra-violet absorption spectra were measured (Figs. 1 and 2). The spots corresponding to the 5′-phosphates of adenosine and uridine showed ultra-violet absorption spectra typical for these substances. Furthermore, the cytidine derivative showed a maximum at 279 and a minimum at 240 mμ in acid, and a maximum at 272 and minimum at 249 mμ in alkali, in good agreement with values for cytidine phosphates (Ploeser and Loring, *J. Biol. Chem.*, 1949, **178**, 431). After hydrolysis with perchloric acid (Marshak and Vogel, *ibid.*, 1951, **189**, 597; Wyatt, *Biochem. J.*, 1951, **48**, 584) the adenosine, uridine, and cytidine derivatives yielded the bases adenine, uracil, and cytosine respectively. These were identified by paper chromatography and measurement of their ultra-violet spectra.

It was found that normal cells of this organism also contain appreciable amounts of these nucleotides. However, identification was somewhat complicated in this case by the presence of large amounts of unidentified cell products which interfere with the paper-chromatographic procedure. Further confirmation of the structure of these substances was sought in a study of their behaviour on an ion-exchange resin column. The nucleotides present in an aqueous extract of the dried organisms were precipitated as their mercury salts (Cabib, Leloir, and Cardini, *loc. cit.*), inorganic phosphate was removed with barium

hydroxide, and then the soluble barium salts were separated by chromatography on Dowex-1 resin (chloride form). Separation of components was effected by elution with 0·002N-hydrochloric acid in the usual manner (Cohn and Carter, *J. Amer. Chem. Soc.*, 1950, **72**, 4276). Nucleotides emerging from the column were detected by measuring the absorption at 260 mμ of samples of eluate. From the diagram (Fig. 3) it can be seen that a strongly absorbing substance was eluted before adenosine-5′ phosphate. This is in the position expected for cytidine-5′ phosphate (Cohn and Carter, *loc. cit.*). A smaller peak corresponding to uridine-5′ phosphate followed adenosine-5′ phosphate.

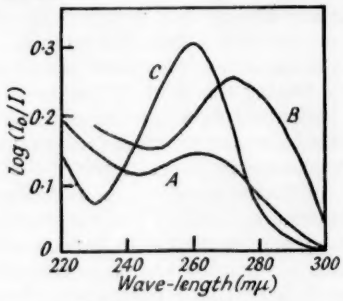
When examined on paper these nucleotides were indistinguishable from synthetic samples of the 5′-phosphates of cytidine, adenosine, and uridine (kindly supplied by Pro-

FIG. 1. *Absorption spectra of nucleotides from dried cells of* L. arabinosus *in* 0·01N-*hydrochloric acid.*



A, Uridine-5′ phosphate.
B, Cytidine-5′ phosphate.
C, Adenosine-5′ phosphate.

FIG. 2. *Absorption spectra of nucleotides from dried cells of* L. arabinosus *in* 0·01N-*sodium hydroxide.*



A, Uridine-5′ phosphate.
B, Cytidine-5′ phosphate.
C, Adenosine-5′ phosphate.

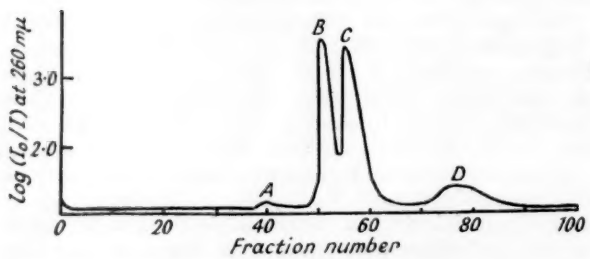


FIG. 3. *Nucleotides from dried* L. arabinosus *eluted from Dowex-1 column with* 0·002N-*hydrochloric acid.*

B, Cytidine-5′ phosphate.
C, Adenosine-5′ phosphate.
D, Uridine-5′ phosphate.

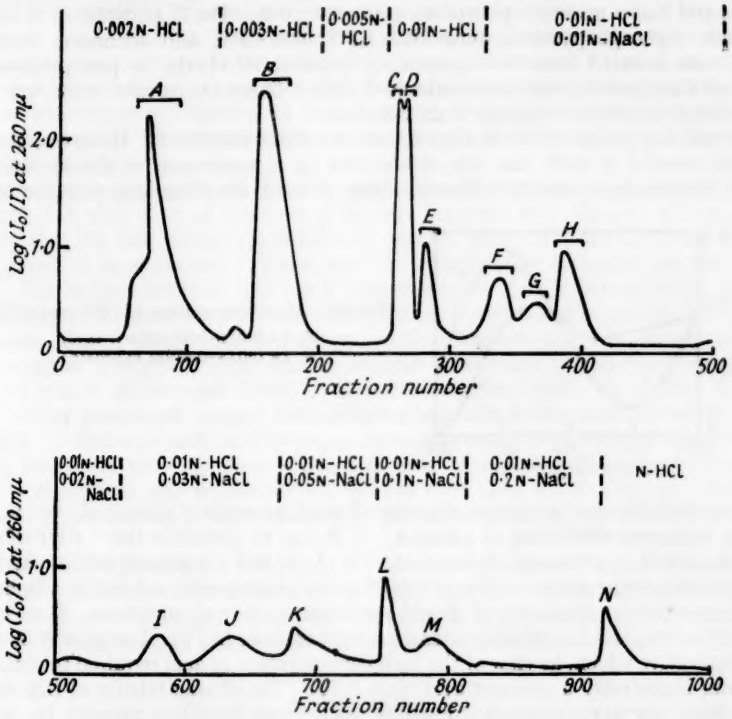
fessor A. R. Todd). They gave typical blue spots after spraying of the paper with periodate followed by Schiff's reagent (Buchanan, Dekker, and Long, *J.*, 1950, 3162), thereby indicating the absence of substituents at positions 2′ and 3′. They also differed from the corresponding nucleoside-2′ and 3′ phosphates in their position on the paper.

The insoluble barium salts obtained from the dried organisms contained much inorganic phosphate. However, after hydrolysis with acid followed by chromatography on paper a rather weak spot was observed which corresponded in position and ultra-violet spectrum with guanine. The nature of the substance giving rise to this purine was not examined further, but it is probable that it was present originally as a guanosine phosphate. It is noteworthy in this connection that guanosine-5′ triphosphate has been isolated recently from natural sources (Bergkvist and Deutsch, *Acta Chem. Scand.*, 1953, **7**, 1307).

It appears from Fig. 3 that relatively large amounts of cytidine-5′ phosphate are present, either free or in some labile combined form, in *L. arabinosus*. At present the only known natural derivative of cytidine is ribonucleic acid. It is true that cytidine-5′ phosphate has been obtained, along with the corresponding 2′- and 3′-phosphate, by ribonuclease

digestion of ribonucleic acid (Cohn and Volkin, *Nature*, 1951, **167**, 483). However, special conditions are required for this type of hydrolysis in order to prevent the action of 5′-phosphatases which occur in many cells. For this and other reasons, we considered it unlikely that the cytidine-5′ phosphate in our preparations had been formed by degradation of ribonucleic acid. Furthermore, no 2′- or 3′-phosphates were present in the extracts, and these would be expected if ribonucleic acid was being hydrolysed during the preparation of the dry cells. It seemed probable that the nucleotide was either a nucleic acid precursor or a hydrolysis product of hitherto unknown cytidine-containing intermediates or co-enzymes.

FIG. 4. *Elution of nucleotides from fresh cells on Dowex-1.*



A, DPN. *B, Adenosine-5′ phosphate. C and D*, CPX *and* CPY. *E, Uridine-5′ phosphate. F, Guanine derivative. G, Adenine derivative. H*, ADP. *I, J, K, L, Uridine derivatives.* M, N, *Adenine derivatives.*

The nucleotides present in the dried organisms were probably formed by the action of phosphatases on various more complex coenzymes. Consequently, a more detailed examination of heat-killed organisms was undertaken. It was considered that phosphatases would be destroyed by this treatment. Rapidly growing cells were harvested and immediately extracted with boiling aqueous alcohol. The nucleotides were precipitated as their mercury salts which were then converted into ammonium salts, and the mixture was resolved on Dowex-1. As expected, the elution diagram (Fig. 4) indicated that several pyrophosphates were present in rapidly killed cells which were absent from the dried organisms.

Substance *A* was eluted with 0·002N-acid. It was identified as diphosphopyridine nucleotide (DPN) by its position on the diagram, its absorption spectrum, and the characteristic spectral changes shown in the presence of potassium cyanide. Substance *B*, eluted with 0·003N-acid, was identified as adenosine-5′ phosphate. It showed maximum

absorption at 260 mμ, yielded adenine on acid hydrolysis, and was indistinguishable from the 5′-phosphate on paper. It gave a positive periodate–Schiff test and contained adenine and phosphorus in the ratio approx. 1 : 1. It is interesting to note that no cytidine-5′ phosphate was eluted up to this point. If this nucleotide were present in these extracts it should have appeared between DPN and adenosine-5′ phosphate. Peaks *C* and *D*, although incompletely resolved, represent two substances with typical cytidine spectra. These substances, which have been called CPX and CPY, are discussed in more detail below. They probably represent the source of cytidine-5′ phosphate present in the dried organisms. *E* followed *C* and *D* rather closely. It was identified as uridine-5′ phosphate by the absorption spectrum, comparison with synthetic uridine-5′ phosphate on paper, and by the positive periodate–Schiff reaction; the substance gave uracil after acid hydrolysis and had a uridine : phosphate ratio of 1 : 0·9. The 5′-phosphates of adenosine and uridine, diphosphopyridine nucleotide, CPX and CPY, and adenosine diphosphate (peak H) were isolated from the appropriate fractions of eluate by precipitation of the mercury salts and conversion into ammonium salts. Other nucleotides were not present in large enough amounts to permit their isolation.

The remaining peaks shown in Fig. 4 were not fully identified. However, the nature of the base present in each case was established by measurement of absorption spectra. With this information, tentative identification of most fractions was possible by direct

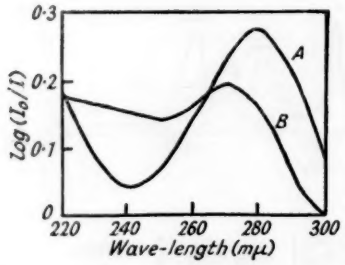


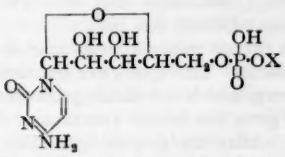
FIG. 5. *Absorption spectra of* CPX *and* CPY.
A, In 0·01N-*hydrochloric acid.*
B, In 0·01N-*sodium hydroxide.*

comparison with the similar elution diagram of yeast extracts (Cabib *et al., loc. cit.*). *F* is due to an unknown derivative of guanine. *G* is due to probably the " ADP-ribose " of Cabib *et al.*, and *H* to adenosine diphosphate. *I*, *J*, *K*, and *L* represent uridine derivatives, *I* and *J* possibly being uridine diphosphate-*N*-acetylglucosamine and uridine-diphosphate-glucose respectively. Similarly, *L* would represent uridine diphosphate, *K* an unknown uridine derivative, and *M* probably adenosine triphosphate (ATP). The peak *N* is due to an adenine derivative which, in view of the high concentration of acid required to elute it from the column, is probably a stronger acid than ATP. The characteristics of this substance on the column are approximately consistent with those described recently for adenosine tetraphosphate (Marrian, *Biochem. Biophys. Acta*, 1954, **13**, 278) but insufficient material corresponding to this peak has been available to enable reliable characterisation.

In a preliminary report of this work (Baddiley and Mathias, *Chem. and Ind.*, 1954, 277) we had not recognised the dual nature of peaks *C* and *D*. Consequently, early experiments on the nature of CPX and CPY were performed on a mixture of the two substances. This is unimportant as far as the identification of the pyrimidine nucleotide part of the molecule is concerned since both yield cytidine-5′ phosphate on hydrolysis in N-hydrochloric acid for 10 min. at 100°. No other nucleotide was present in the hydrolysate. Cytidine-5′ phosphate was identified by comparison with the authentic nucleotide on paper chromatography in two solvents, by its spectrum, and by hydrolysis to cytosine. The materials CPX and CPY, and the cytidine phosphate obtained from them by acid hydrolysis, gave positive periodate–Schiff tests on paper. Only one spot, corresponding to cytidine-5′ phosphate, was observed by this technique on chromatograms of the acid-hydrolysis products of CPX and CPY. This indicates that positions 2′ and 3′ are unsubstituted in both CPX and CPY. The ultra-violet absorption spectra, determined on fractions corresponding to the maxima *C* and *D*, were identical. The positions of maxima and minima

in acid and alkali (Fig. 5) correspond closely with those for cytidine and its phosphates. It is unlikely then that the residues X and Y are directly attached to the pyrimidine ring.

The two cytidine derivatives accompanied inorganic phosphate when eluted from the column. However, as paper chromatography indicated the absence of other organic phosphates, it was possible to determine the ratio of cytidine to organic phosphate in the combined substances. A value of almost exactly 1 : 1 was obtained. Very similar values were observed from analyses of spots of CPX and CPY eluted from a paper chromatogram in *n*-propyl alcohol–ammonia. In this solvent mixture inorganic phosphate was separated from the phosphoric esters. No inorganic phosphate was liberated on hydrolysis of these substances in N-hydrochloric acid at 100° for 15 min. It is clear then that CPX is a derivative of cytidine-5′ phosphate in which a group X is joined in ester linkage with the phosphate residue according to the annexed formula. Similarly, CPY must be represented by a corresponding formula in which X has been replaced by Y. These substances are unusual in that, although from their nature it is probable that they are coenzymes or intermediates, all known nucleotide coenzymes are esters of pyrophosphoric acid.



It has not yet been possible on the very small amounts of material available to determine the nature of X and Y or of the type of linkage involved with the rest of the molecule. It is likely that the two groups are chemically similar, since CPX and CPY run as a single spot on paper in most solvent systems and are incompletely separated on the Dowex-1 column. The linkage between cytidine-5′ phosphate and X or Y is very labile, since both are completely hydrolysed to cytidine-5′ phosphate in N-hydrochloric acid at 100° in 10 min. Furthermore, almost complete hydrolysis to the 5′-phosphate occurred during attempts to remove inorganic phosphate from these substances by chromatography on Dowex-1 in the presence of borate (Khym and Cohn, *J. Amer. Chem. Soc.*, 1953, **75**, 1153). It appears that the rather prolonged contact with dilute alkali which this method entails removes both X and Y : this was confirmed by paper chromatography in *n*-propyl alcohol–ammonia. Although the main spot on these chromatograms represented the mixed esters, some cytidine-5′ phosphate was produced. It follows that they are not simple alkyl esters. Also X and Y contain no phosphorus and do not show marked absorption in ultra-violet light.

Some degree of separation of CPX and CPY has been obtained by paper chromatography in *iso*butyric acid–ammonium *iso*butyrate–water. However, it has not yet been possible to decide which of the two spots produced corresponds to a particular peak on the elution diagram. Further work on the nature of these nucleotides is in progress.

Experimental

Whatman No. 4 paper, washed with 2N-acetic acid, was used throughout this work.

Preliminary Examination of Cystine-deficient Cells.—Washed cells (1·06 g.) which had been dried over phosphoric oxide were suspended in water (10 c.c.), kept at 0° for 2 hr. with occasional stirring, and finally heated at 100° for 5 min. The cell debris was removed by centrifugation and extracted twice with water. The combined supernatant liquors were freeze-dried. A portion of the extract (95 mg.) was dissolved in water (1 c.c.), and saturated barium hydroxide solution was added cautiously until precipitation was complete. The precipitate was centrifuged off and washed with water. The combined supernatant liquid and washings were passed through a column of Amberlite IRC–50 resin (H^+ form) (0·6 cm.^{2} × 17 cm.). The acidic effluent was neutralised with ammonia and evaporated to dryness under reduced pressure. The residue was dissolved in water (0·1 c.c.) and applied to the base-line of a paper chromatogram as a band (16 cm. long). Appropriate authentic nucleotides were applied at each end of the band. The chromatogram was developed with *iso*butyric acid–ammonium *iso*butyrate–water (Magasanik, Vischer, Doniger, Elson, and Chargaff, *J. Biol. Chem.*, 1950, **186**, 37), dried in warm air, and examined under a Mineralight lamp. Two narrow vertical strips were cut out and examined with the periodate–Schiff spray and with a phosphate spray reagent (Hanes and Isherwood, *Nature*, 1949, **164**, 1107). Several bands were observed which absorbed ultra-

violet light, contained phosphorus, and gave positive periodate–Schiff reactions. Three of these corresponded in position with uridine-5′ phosphate (R_F 0·35), cytidine-5′ phosphate (R_F 0·41), and adenosine-5′ phosphate (R_F 0·51).

Identification of Uridine-5′ Phosphate.—The band (R_F 0·35) was cut out and eluted from the paper by steeping it in water (5 c.c.) for 2 hr. Paper was removed and the solution was evaporated to dryness in a desiccator. The residue was dissolved in water (0·1 c.c.) and a portion diluted to 2 c.c. with 0·01N-hydrochloric acid. The ultra-violet absorption spectrum (Fig. 1) was measured in a 1 cm. cell in a Hilger " Uvispek," ($\lambda_{max.}$ 262 mμ; $\lambda_{min.}$ 231 mμ). Sufficient N-sodium hydroxide was added to give a solution 0·01N with respect to sodium hydroxide, and the spectrum was re-examined ($\lambda_{max.}$ 261 mμ; $\lambda_{min.}$ 242 mμ) (Fig. 2). The spectra closely resemble those reported for uridylic acid (Ploeser and Loring, *loc. cit.*).

Only one absorbing spot was observed when this fraction was run on paper in *iso*propanol–hydrochloric acid–water (Wyatt, *loc. cit.*) and in *n*-propanol–ammonia. This spot gave positive reactions for organic phosphate and with the periodate–Schiff spray, and was indistinguishable from uridine-5′ phosphate. Uridylic acid from yeast did not give the latter reaction and moved faster than the 5′-phosphate in both solvent systems. After hydrolysis with 72% perchloric acid it gave uracil, identified by its R_F in *iso*propanol–hydrochloric acid and by its absorption spectrum ($\lambda_{max.}$ 259 mμ, $\lambda_{min.}$ 230 mμ in 0·01N-hydrochloric acid; $\lambda_{max.}$ 282 mμ, $\lambda_{min.}$ 242 mμ in 0·01N-sodium hydroxide).

Identification of Cytidine-5′ Phosphate.—The band (R_F 0·41) was eluted and the absorption spectrum measured in the same way as for uridine-5′ phosphate. It corresponded closely with that of cytidylic acid. The substance was indistinguishable from cytidine-5′ phosphate on paper chromatography in *iso*butyric acid–ammonium *iso*butyrate–water, *n*-propanol–ammonia, and *iso*propanol–hydrochloric acid, in all of which it gave a single spot containing phosphorus and giving a positive reaction with the periodate–Schiff reagent. Cytidylic acid moved faster than the 5′-phosphate in these solvents (see Table). After hydrolysis with perchloric acid it yielded cytosine, identified by paper chromatography in *iso*propanol–hydrochloric acid and by its absorption spectrum ($\lambda_{max.}$ 274 mμ, $\lambda_{min.}$ 239 mμ in 0·01N-hydrochloric acid; $\lambda_{max.}$ 271 mμ, $\lambda_{min.}$ 249 mμ in 0·01N-sodium hydroxide).

Identification of Adenosine-5′ Phosphate.—The band (R_F 0·51) had an absorption spectrum typical of adenosine phosphates ($\lambda_{max.}$ 259 mμ, $\lambda_{min.}$ 232 mμ in 0·01N-hydrochloric acid; $\lambda_{max.}$ 260 mμ, $\lambda_{min.}$ 232 mμ in 0·01N-sodium hydroxide). The substance gave a single spot in the above-mentioned solvent systems and was indistinguishable from adenosine-5′ phosphate. After hydrolysis with perchloric acid it gave adenine ($\lambda_{max.}$ 263 mμ, $\lambda_{min.}$ 230 mμ in 0·01N-hydrochloric acid; $\lambda_{max.}$ 262 mμ, $\lambda_{min.}$ 231 mμ in 0·01N-sodium hydroxide).

Examination of Dried Normal Cells of L. arabinosus.—The dried cells were extracted by a method similar to that adopted for the cystine-deficient organisms. Direct paper chromatography of this extract was not satisfactory, so nucleotides were precipitated before examination in the following manner. A 5% solution of the extract in aqueous alcohol (50%) was adjusted to pH 5 with dilute nitric acid, and a solution of mercuric acetate in acetic acid (Caputto, Leloir, Cardini, and Paladini, *loc. cit.*) was added dropwise until no further precipitation occurred. The precipitate was centrifuged off, washed with aqueous alcohol, suspended in water, and decomposed with hydrogen sulphide. Mercuric sulphide was removed by centrifugation and washed with water. The supernatant liquid and washings were combined, aerated, adjusted to pH 7 with aqueous ammonia, and freeze-dried. Identification of the nucleotides was carried out by paper chromatography and ultra-violet spectroscopy in the same manner as for those from cystine-deficient cells. The 5′-phosphates of uridine, cytidine, and adenosine were present. No other nucleotides were observed.

Ion-exchange Chromatography of Nucleotides from Dried Normal Cells (see Fig. 3).—The freeze-dried ammonium salts obtained from the insoluble mercury salts (*ca.* 0·1 g.) described above were dissolved in water (2 c.c.), and saturated barium hydroxide solution was added until precipitation ceased. The precipitate was removed by centrifugation and washed with water (2 × 2 c.c.). The combined supernatant liquid and washings were adjusted to pH 7·5 with acetic acid and passed through a column (0·5 cm.^{2} × 7 cm.) of Dowex-1 resin (chloride form, 200—400 mesh). After thorough washing with water, elution was commenced with 0·002N-hydrochloric acid at 0·3 c.c./min. The eluate was collected in 6-c.c. fractions on an automatic fraction-collector, and the extinction coefficient at 260 mμ of each fraction was measured. Three main peaks, designated *B*, *C*, and *D* in order of elution, were observed (Fig. 3). The fractions corresponding to the peaks were combined and adjusted to pH 5 with ammonia solution. Several drops of the mercuric acetate reagent were added to each, and the solutions were kept

at 0° overnight. The precipitates were centrifuged off and washed with 50% alcohol, and individual nucleotides were regenerated as before. The resulting solutions were freeze-dried as ammonium salts. The spectra of "peak tubes" (diluted appropriately) and the R_P values (see Table) indicated that *B*, *C*, and *D* represented the 5′-phosphates of cytidine, adenosine, and uridine respectively.

Growth and Extraction of Fresh Cells.—*L. arabinosus* 17–5 was grown at 37° on the following medium: glucose 2%, "Pronutrin" (Herts Pharmaceuticals Ltd.) 2%, hydrated sodium acetate 1%, yeast extract (1 part of yeast, 4 parts of water; boiled for 10 min. and filtered) 200 c.c./l., potassium dihydrogen phosphate 0·45%, N-sodium hydroxide 26·0 c.c./l., and inorganic salts "B" (Barton-Wright, "Practical Methods for the Microbiological Assay of Vitamin B Complex and Essential Amino Acids," London, Ashe Laboratories, 1946) 5·0 c.c./l. The medium was sterilised in the autoclave. The organism, supplied as a stab-culture, was sub-cultured on the above medium for 7 days with daily transfer. An inoculum (500 c.c.) was grown for 24 hr. and used to inoculate 3 flasks each containing 4 l. of medium. After growing for 24 hr. the cells were harvested in a Sharples centrifuge. The wet cells (65—70 g.) were heated immediately with constant stirring in a mixture of 96% alcohol (70 c.c.) and 50% alcohol (140 c.c.) until the suspension boiled. The mixture was boiled for 5 min., then cooled to room temperature, and cell debris were removed by centrifugation. The precipitate was re-extracted with 30% alcohol (140 c.c.), and the combined extracts were submitted to mercury-salt precipitation as described before. The nucleotides were obtained as freeze-dried ammonium salts (*ca.* 1·25 g.).

A sample (*ca.* 5 mg.) was hydrolysed with 72% perchloric acid, and the hydrolysate run on paper in *iso*propanol–hydrochloric acid. Four spots were detected in ultra-violet light. These were identified by their R_F values and absorption spectra as adenine, uracil, cytosine, and guanine. From their extinction coefficients they were shown to be present in the approximate proportions 15 : 9 : 5 : 1 respectively.

Chromatography of Nucleotides from Fresh Cells on Dowex-1.—A sample of the ammonium salts (500 mg.) in water (350 c.c.) was adsorbed on a column of Dowex-1 (chloride form, 200—400 mesh, 1·4 cm.^{2} × 21 cm.). The column was washed with water, until the absorption of the eluate had fallen to 0·1 optical-density unit. Elution with 0·002N-hydrochloric acid was commenced and the eluate was collected in 6·6-c.c. fractions at 0·28 c.c./min. The absorption spectra of the peak solutions were measured on samples from the peak tubes. The nucleotides corresponding to the peaks were isolated through their mercury and ammonium salts in the manner described before. This technique was unsuccessful for peaks *I* onwards, probably owing to the extreme dilution of these nucleotides together with the high salt concentration.

Identification of Peaks from Column (see Fig. 4).—*Peak A* (*diphosphopyridine-nucleotide*). This substance had a typical adenine spectrum. On the addition of potassium cyanide there was a marked fall in the absorption at 260 mμ and appearance of a peak at 325 mμ. This behaviour is typical of a pyridine-nucleotide (Colowick, Kaplan, and Ciotti, *J. Biol. Chem.*, 1951, **191**, 447). Paper chromatography in ethanol–ammonium acetate–water (pH 7·5) (Paladini and Leloir, *Biochem. J.*, 1952, **51**, 426) and in *iso*butyric acid–ammonium *iso*butyrate–water (R_F 0·4) indicated that a minor component was present which also contained phosphorus. From the spectral and ion-exchange characteristics of the main component of peak *A* it is concluded that this is diphosphopyridine-nucleotide. This, and all other substances from the column which were isolated through their mercury salts (peaks *A*—*E*, and *H*), absorbed ultra-violet light, contained phosphorus and showed a positive periodate–Schiff reaction on paper.

Peak B (*adenosine-5′ phosphate*). This had an adenine spectrum. It was indistinguishable from synthetic adenosine-5′ phosphate on paper chromatography (see table of R_F values). A minor non-absorbing organic phosphate was also present (R_F 0·23 in the *iso*butyric acid solvent). The main spot was cut out and eluted from the paper. A blank spot of corresponding position on the paper was treated similarly. The "adenine" content of the eluate was determined from the extinction coefficient and organic phosphate was determined by Allen's method (*Biochem. J.*, 1940, **34**, 858). A ratio adenine : phosphorus of 1 : 0·9 was found, in good agreement with the expected value for adenosine-5′ phosphate.

Peaks C and D (CPX *and* CPY). These peaks were poorly separated. The substances showed identical spectra ($\lambda_{max.}$ 280 mμ, $\lambda_{min.}$ 241 mμ in 0·01N-hydrochloric acid; $\lambda_{max.}$ 272 mμ, $\lambda_{min.}$ 250 mμ in 0·01N-sodium hydroxide), typical for cytidine derivatives. In the early chromatograms in *iso*butyric acid–ammonium *iso*butyrate–water the substances appeared to give a single spot (R_F 0·23), moving at approximately half the speed of cytidine-5′ phosphate (R_F 0·41), and at the same speed as inorganic phosphate, which was readily detected in both fractions

by the yellow colour produced immediately when the paper was sprayed with the ammonium molybdate reagent. Spots from *C* and *D*, and spots of corresponding area and R_F from blank tracks, were cut out and eluted from such a paper with 0·01N-hydrochloric acid. The cytidine content of the eluate was determined from its absorption at 280 mμ; also the total and inorganic phosphate content was measured. For *C* a ratio of cytidine : organic phosphate of 1 : 1·005 was found, and for *D* the ratio was 1 : 1·04. Samples of a similar eluate in N-hydrochloric acid were heated at 100° for 10 min. and inorganic phosphate was determined. A ratio of cytidine : labile phosphate of 1 : 0·03 for *C*, and 1 : 0·08 for *D* was obtained. Unheated samples were used as controls. This indicates that no inorganic phosphate is liberated by such treatment. Similar results were obtained from analyses on the substances from *C* and *D*. Samples were dissolved in 0·01N-hydrochloric acid (3 c.c.). Samples (0·5 c.c.) of each solution were diluted to 2 c.c. with 0·01N-hydrochloric acid and the absorptions at 280 mμ were measured. Aliquot portions (0·7 c.c.) were used for total, inorganic, and labile phosphate determinations. Labile phosphate was determined by adding concentrated hydrochloric acid (0·07 c.c.) and then heating at 100° for 15 min. For *C* the ratio cytidine : organic phosphate : labile phosphate was 1 : 1·02 : 0·1 and for *D* 1 : 1·02 : 0·01. Very similar values were found when the method of Lowrey and Lopez (*J. Biol. Chem.*, 1946, **102**, 41) was used for inorganic and labile phosphate determinations. This eliminates the possibility that hydrolysis of a very labile phosphate had occurred before or during the inorganic phosphate determinations by Allen's method.

Hydrolysis of material from *C* and *D* with perchloric acid gave cytosine, identified by paper chromatography and from its absorption spectrum. With N-hydrochloric acid at 100° (10 min.) both substances were converted into cytidine-5′ phosphate, identified by paper chromatography in the solvents shown in the Table. No other phosphates or substances absorbing ultra-violet light were observed on the papers.

R_F values.

The values given are averages. Individual values varied because of lack of temperature control. In all cases authentic nucleotides were run as controls. Ascending-front chromatography was used throughout, and solvent mixtures were freshly prepared.

	Pr^{i}·CO_2H–NH_3–H_2O	$Pr^{n}OH$–NH_3–H_2O (6 : 3 : 1)	EtOH–$AcONH_4$–H_2O, pH 7·5
Cytidine-5′ phosphate	0·41	0·27	—
Cytidine-3′ phosphate (*b*)	0·47	0·34	—
CPX, CPY	0·18, 0·22	0·38	0·17
Adenosine-5′ phosphate	0·51	0·33	—
Adenosine-3′ phosphate (*b*)	0·58	0·39	—
ADP	0·42	—	—
Uridine-5′ phosphate	0·30	0·23	—
Uridine-3′ phosphate (*b*)	0·35	0·30	—

Substances from *C* and *D* were separated from inorganic phosphate by chromatography in *n*-propanol–ammonia–water. The main spot and a blank area were cut out and eluted with 0·01N-hydrochloric acid. Analysis as before gave a ratio of cytidine : organic phosphate : labile phosphate 1 : 1·08 : 0·1. Re-chromatography of the main spot in the *iso*butyric acid solvent indicated that some hydrolysis to cytidine-5′ phosphate had occurred.

Peak E (*uridine-5′ phosphate*). This material gave a uridine spectrum. Paper chromatography (see Table) indicated that only one substance was present which was indistinguishable from uridine-5′ phosphate. The ratio uridine : organic phosphate was 1 : 0·9, in good agreement for a uridine monophosphate.

Peak F. The absorption spectrum of this material was very similar to that of guanylic acid. However, it was not precipitated by mercuric acetate and has not been examined further.

Peak G. An adenine spectrum was given by this material. From its position on the elution diagram it corresponds to the " ADP-ribose " of Cabib *et al.* (*loc. cit.*), but complete identification is still required.

Peak H (*adenosine-5′ pyrophosphate*, ADP). This material also gave an adenine spectrum. The ratio adenine : organic phosphate was 1 : 1·8 and the substance was indistinguishable from synthetic adenosine-5′ pyrophosphate (ADP) on paper chromatography in the *iso*butyric acid system and in disodium hydrogen phosphate–*iso*amyl alcohol–water (Carter, *J. Amer. Chem. Soc.*, 1950, **72**, 4274).

Peaks, I, J, K, and L. These materials had uridine spectra. They were not characterised further.

Peaks M and N. These materials were adenine derivatives.

Examination of CPX *and* CPY *on Dowex*-1 *in the Presence of Borate.*—A solution of the mixed substances (30 mg.) in water (25 c.c.) was passed through a column (1·4 cm.^{2} × 21 cm.) of Dowex-1 (chloride form, 200—400 mesh). After washing with water (50 c.c.) elution with 0·025M-ammonium chloride and 0·01M-sodium borate was commenced. Fractions of eluate were examined for absorption at 260 mμ and for the presence of inorganic phosphate. The latter emerged as a fairly sharp peak (vol. to max., 1270 c.c.). The borate washing lasted for 4 days, during which the optical density remained below 0·05 unit. After removal of inorganic phosphate nucleotides were eluted with 0·005N-hydrochloric acid. Two peaks were detected. Paper chromatography of the first, strong peak indicated the presence of cytidine-5′ phosphate, whereas the second, weak peak was due to the CPX and CPY mixture.

Thanks are extended to Dr. D. E. Hughes for a culture of *L. arabinosus* and for information about its growth. This work was supported by a grant from the Nuffield Foundation.

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Synthesis of 2 : 4 : 6-*Trishydroxymethylphenol and of* 2 : 4 : 6-*Trishydroxybenzylphenol Derivatives.*

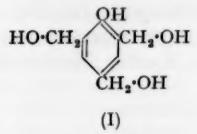
By A. T. CARPENTER and R. F. HUNTER.

[Reprint Order No. 5004.]

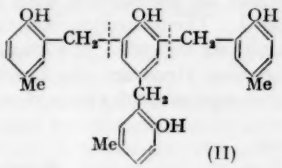
2 : 4 : 6-Trishydroxymethylphenol has been synthesised from 2 : 4-diformylphenol by way of 2-chloromethyl-4 : 6-diformylphenol, hydrolysis to the corresponding hydroxymethyl derivative, and subsequent reduction with platinum and hydrogen, and by a modification of this route involving dichloromethylation of salicylaldehyde with subsequent hydrolysis and reduction of 2-formyl-4 : 6-bishydroxymethylphenol. The trialcohol has also been prepared by reduction of 2 : 4 : 6-trisacetoxymethylphenyl acetate with lithium aluminium hydride.

Confirmation of the constitution of tetranuclear Novolaks formed by condensation of 2 : 4 : 6-trishydroxymethylphenol and 2 : 4 : 6-trisacetoxymethylphenyl acetate with *p*-substituted phenols has been provided by synthesis of 2 : 4 : 6-tri-(2-hydroxy-3 : 5-dimethylbenzyl)phenol from 4-bromo-2 : 6-di-(2-hydroxy-3 : 5-dimethylbenzyl)phenol by a lithium exchange reaction, reduction of the 4-carboxy-phenol with lithium aluminium hydride, and condensation of the resulting hydroxymethyl derivative with 2 : 4 : 1-xylenol.

THE isolation of 2 : 4 : 6-trishydroxymethylphenol (I) which had figured for several years in reviews and standard works on plastics as a crystalline individual was announced at the Symposium on Polymer Chemistry as Applied to Plastics in 1950. The trialcohol was obtained in small yield by reduction of ethyl trimesate with lithium aluminium hydride in dioxan and characterised by the tetranuclear Novolak (II) obtained by condensation with



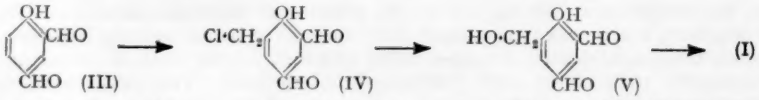
(I)



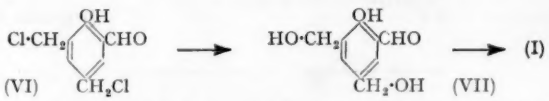
(II)

p-cresol (Carpenter and Hunter, *J. Appl. Chem.*, 1951, **1**, 217). Attempts to prepare 2 : 4 : 6-trishydroxymethylphenol by reduction of 2 : 4 : 6-trisacetoxymethylphenyl acetate obtained by Bruson and MacMullen's method (*J. Amer. Chem. Soc.*, 1941, **63**, 270) with

lithium aluminium hydride in ether proved unsuccessful (*loc. cit.*). From material purified by high-vacuum distillation, however, we obtained quite substantial yields of the trialcohol from the trisacetoxymethyl derivative.

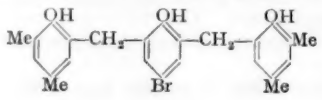


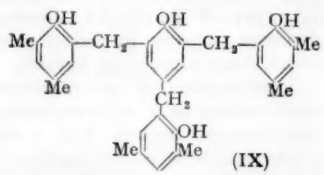
The rational synthesis of the trialcohol from 2 : 4-diformylphenol (III) by way of 2-chloromethyl-4 : 6-diformylphenol (IV) and subsequent hydrolysis to the hydroxymethyl derivative (V) and catalytic reduction of the latter with platinum is now described. This route, from salicylaldehyde as starting material, was modified by direct introduction of two chloromethyl groups into the latter to give the dichloromethyl derivative (VI), which was



hydrolysed to 2-formyl-4 : 6-bishydroxymethylphenol (VII) and then reduced to the trialcohol.

The constitution of tetranuclear Novolaks obtained by condensation of the trialcohol and 2 : 4 : 6-trisacetoxymethylphenyl acetate with *p*-substituted phenols has been confirmed by synthesis of 2 : 4 : 6-tri-(2-hydroxy-3 : 5-dimethylbenzyl)phenol (IX) from 4-bromo-2 : 6-di-(2-hydroxy-3 : 5-dimethylbenzyl)phenol (VIII) by a lithium exchange reaction to give the acid (VIII with CO_2H in place of Br), reduction with lithium aluminium hydride to the corresponding hydroxymethyl derivative, and condensation of the last with 2 : 4 : 1-xylenol to give the tetranuclear compound (IX) identical with that obtained from 2 : 4 : 6-trisacetoxymethylphenyl acetate and 2 : 4 : 1-xylenol.





In an unsuccessful attempt to prepare 2 : 4 : 6-tri-(2-hydroxy-5-methylbenzyl)phenol (II) from 2 : 4 : 6-trisacetoxymethylphenyl acetate and *p*-cresol in which heating was conducted for a longer period, a small amount of 2 : 7-dimethylxanthen was formed, and in later experiments was accompanied by larger amounts of 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane which is presumably the precursor of the former (cf. Megson, *J. Soc. Chem. Ind.*, 1939, **58**, 131). The effect of prolonged heating of 2 : 4 : 6-tri-(2-hydroxy-5-methylbenzyl)phenol with *p*-cresol in the presence of hydrochloric acid was therefore examined. By high-vacuum distillation fractions were separated containing both 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane and 2 : 4′-dihydroxy-5-methyldiphenylmethane which was identified by comparison with a specimen synthesised from *p*-hydroxybenzyl alcohol and *p*-cresol. The formation of these two-ring molecules may be attributed to bond fission at the positions indicated in formula (II) with subsequent reaction with *p*-cresol. It may be noted that these are the bonds which would be expected from ultra-violet absorption spectroscopical results to be sterically hindered (Hunter, Morton, and Carpenter, *J.*, 1950, 441).

Experimental

Reduction of 2 : 4 : 6-*Trisacetoxymethylphenyl Acetate to* 2 : 4 : 6-*Trishydroxymethylphenol by Lithium Aluminium Hydride.*—The oil (50 g.) obtained by treatment of 2 : 4 : 6-tri(dimethylaminomethyl)phenol with acetic anhydride following Bruson and MacMullen's directions

(*loc. cit.*) was distilled at 10^{-3} mm. from a retort and three fractions were collected : b. p. 180—185° (furnace-temp.), n_D^{21} 1·5023 (8 g.); b. p. 185—190°, n_D^{21} 1·5026 (28 g.); b. p. 190—195°, n_D^{21} 1·5025 (10 g.). The two later fractions were used for reduction experiments. The tetra-acetate (2·5 g.) in ether (25 c.c.) was treated with lithium aluminium hydride (5 g.) in ether (25 c.c.). After subsidence of a vigorous reaction, the mixture was heated under reflux for 3 hr. and kept overnight at room temperature. After decomposition of excess of reagent with water in ether and acidification with dilute sulphuric acid, sufficient sodium carbonate was added to start precipitation and the mixture was extracted with ethyl acetate. Evaporation of the united extracts under reduced pressure furnished an oil which when washed with benzene crystallised in needles (0·5 g.) which on recrystallisation from ethyl acetate gave 2 : 4 : 6-trishydroxymethylphenol, m. p. 75—78° (0·28 g.) undepressed by admixture with a specimen prepared by reduction of ethyl trimesate. On further recrystallisation from ethyl acetate the trialcohol was obtained in fine flakes, m. p. 79—82°.

2-Chloromethyl-4 : 6-diformylphenol.—A mixture of 2 : 4-diformylphenol (Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2141) (1 g.), trioxan (1 g.), concentrated hydrochloric acid (5 c.c.), acetic acid (5 c.c.), and powdered zinc chloride (3 g.) was saturated with dry hydrogen chloride at 10° and thereafter heated (closed vessel) at 35° for 72 hr. and then at 55° for a further 24 hr., and finally cooled and poured into water. *2-Chloromethyl-4 : 6-diformylphenol* was obtained in small pink crystals (0·7 g.), m. p. 97—100°, which on recrystallisation from *cyclo*hexane furnished colourless plates, m. p. 112—113° (Found : C, 54·7; H, 3·7; Cl, 18·3. $C_9H_7O_3Cl$ requires C, 54·4; H, 3·5; Cl, 17·9%). *2 : 4-Diformyl-6-hydroxymethylphenol* was obtained by keeping a solution of the 6-chloromethyl derivative in 50% aqueous acetone at room temperature for 24 hr. and removing acetone under reduced pressure. On recrystallisation from benzene it formed prisms, m. p. 129—130° (Found : C, 59·7; H, 4·7. $C_9H_8O_4$ requires C, 60·0; H, 4·45%). The diformylhydroxymethylphenol (0·18 g.) was hydrogenated in the usual way with platinum oxide (0·05 g.) in alcohol (10 c.c.). The uptake after 2½ hr. was that required for reduction of two aldehyde groups, and the product on recrystallisation from ethyl acetate furnished 2 : 4 : 6-trishydroxymethylphenol in cream-coloured flakes, m. p. 80—82°, undepressed by admixture with the specimen obtained by reduction of 2 : 4 : 6-trisacetoxymethylphenyl acetate.

Synthesis of 2 : 4 : 6-*Trishydroxymethylphenol from* 3 : 5-*Bischloromethylsalicylaldehyde.*—3 : 5-*Bischloromethylsalicylaldehyde.* A mixture of salicylaldehyde (2 g.), trioxan (1 g.), acetic acid (4 c.c.), zinc chloride (2 g.) and concentrated hydrochloric acid (4 c.c.) was saturated at 10° with hydrogen chloride. After an hour, when precipitation of the monochloromethyl derivative had occurred, the mixture was sealed and heated at 35° for 72 hr. On dilution with water the *bischloromethyl* derivative was obtained in quantitative yield and having m. p. 90—94°; on recrystallisation from light petroleum it formed needles, m. p. 98—99° (Found : C, 49·0; H, 4·0; Cl, 31·9. $C_9H_8O_2Cl_2$ requires C, 49·3; H, 3·7; Cl, 32·4%). The preparation was repeated on a larger scale with slightly varying conditions, the most satisfactory yield (53%) being obtained from salicylaldehyde (72 g.), trioxan (60 g.), zinc chloride (60 g.), hydrochloric acid (240 c.c.), and acetic acid (240 c.c.). *2-Formyl-4 : 6-bishydroxymethylphenol* was prepared by vigorously stirring the bischloromethylsalicylaldehyde in small batches (6 g.) with boiling water (300 c.c.) for 5 min. and extracting the combined solutions with ethyl acetate in a liquid-extraction apparatus at room temperature at 80 mm. for 11 hr. On recrystallisation from ethylene dichloride, the bishydroxymethyl derivative separated in small prisms, m. p. 119—121° (Found : C, 59·0; H, 5·8. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). The yields in larger-scale preparations (58 g. and 48 g. of bischloromethylsalicylaldehyde) were 37 and 56% respectively. On being heated with water for 10 min., the crude bischloromethyl derivative yielded a small quantity of a substance readily separated on account of its sparing solubility in ethyl acetate, which, crystallised from glacial acetic acid, had m. p. 220—222° (Found : C, 57·3; H, 4·3; Cl, 19·1. $C_{17}H_{14}O_4Cl_2$ requires C, 57·8; H, 4·0; Cl, 20·1%). This is probably 3 : 3′-*bischloromethyl-5 : 5′-diformyl-4 : 4′-dihydroxydiphenylmethane.* The bishydroxymethylformylphenol (21·05 g.) in alcohol (275 c.c.) with platinum oxide (0·8 g.) absorbed hydrogen corresponding to reduction of a single aldehyde group after 13 hr. Evaporation of alcohol under reduced pressure after removal of catalyst, followed by recrystallisation from ethyl acetate, furnished 2 : 4 : 6-trishydroxymethylphenol in prisms, m. p. 87—89° (16 g., 76%). By further recrystallisation from ethyl acetate this was raised to 89—91° (Found : C, 58·5; H, 6·8. Calc. for $C_9H_{12}O_4$: C, 58·6; H, 6·5%).

Synthesis of 2 : 4 : 6-*Tri-*(2-*hydroxy-*3 : 5-*dimethylbenzyl)phenol from* 2 : 4 : 6-*Trisacetoxymethylphenyl acetate and* 2 : 4 : 1-*Xylenol and from* 4-*Bromo-*2 : 6-*di-*(2-*hydroxy-*3 : 5-*dimethylbenzyl)phenol by Way of* 4-*Hydroxy-*3 : 5-*di-*(2-*hydroxy-*3 : 5-*dimethylbenzyl)benzoic Acid.*—(i) A

mixture of 2 : 4 : 6-trisacetoxymethylphenyl acetate (3·25 g.), 2 : 4 : 1-xylenol (80 g.), and hydrochloric acid (3 c.c.) was heated on a water-bath, under reflux, for 16 hr., the excess of xylenol was removed by distillation in steam, and the residue (4·8 g.) was twice crystallised from toluene. The tetranuclear Novolak was obtained in needles, m. p. 182—183°, which gave unsatisfactory analyses (Found: C, 77·1, 77·1; H, 7·3, 7·3%) and was therefore distilled at 10^{-4} mm. from a retort (2 hr.; 220—260°). Pure 2 : 4 : 6-tri-(2-hydroxy-3 : 5-dimethylbenzyl)-phenol was thereby separated from an impurity of higher vapour-pressure, and had m. p. 185—186° [Found: C, 79·6; H, 7·4%; *M* (micro-Rast), 460. $C_{33}H_{36}O_4$ requires C, 79·8; H, 7·3%; *M*, 496]. The small and more volatile fraction, m. p. 140—141°, was identified as 2 : 2′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenylmethane which after recrystallisation from benzene–light petroleum had m. p. 145—146·5° alone and when mixed with an authentic specimen.

(ii) 4-*Bromo*-2 : 6-*di*-(2-*hydroxy*-3 : 5-*dimethylbenzyl*)*phenol* was prepared by heating 4-bromo-2 : 6-bishydroxymethylphenol (25 g.) and 2 : 4 : 1-xylenol (250 g.) with a small amount of toluene-*p*-sulphonic acid on a water-bath for 5 hr. Sodium carbonate (0·6 g.) was added and the excess of xylenol removed in steam. The residue on recrystallisation from ethylene dichloride furnished the bishydroxydimethylbenzyl derivative in prisms, m. p. 179—181° (11·2 g.) (Found: C, 65·3; H, 5·7; Br, 18·05. $C_{24}H_{25}O_3Br$ requires C, 65·3; H, 5·7; Br, 18·1%). *n*-Butyl-lithium (Gilman and Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515) (0·058 mole in 50 c.c. of ether) was run into a solution of 4-bromo-2 : 6-di-(2-hydroxy-3 : 5-dimethylbenzyl)-phenol (5 g.) in ether (250 c.c.), and the solution was kept for 17 hr., carboxylated by pouring on to solid carbon dioxide, acidified, and extracted with ether. The ethereal solution was washed with water and extracted with 10% aqueous sodium carbonate. 4-*Hydroxy*-3 : 5-*di*-(2-*hydroxy*-3 : 5-*dimethylbenzyl*)*benzoic acid*, obtained on acidification, was recrystallised from glacial acetic acid, then having m. p. 243—245° (0·95 g.) (Found: C, 73·4; H, 6·3. $C_{25}H_{26}O_5$ requires C, 73·8; H, 6·4%). The acid (0·3 g.), in dry ether (180 c.c.), was added to lithium aluminium hydride (1 g.) in a small amount of the same solvent during 5 min. and the mixture was heated under reflux for an hour. The excess of lithium aluminium hydride was decomposed with wet ether, the mixture acidified with dilute sulphuric acid, and the ethereal layer washed with aqueous sodium carbonate. On evaporation of ether and recrystallisation from methanol, the hydroxymethyl derivative was obtained in needles (0·06 g.), m. p. 170—171° (Found: C, 76·7; H, 7·1. Calc. for $C_{25}H_{28}O_4$: C, 76·8; H, 7·2%). A mixture of this (0·03 g.) and 2 : 4 : 1-xylenol (1·3 g.) with a trace of hydrochloric acid was heated for 16 hr. The residue (m. p. 176—179°) obtained after removal of excess of xylenol in steam, on recrystallisation from benzene, furnished 2 : 4 : 6-tri-(2-hydroxy-3 : 5-dimethylbenzyl)phenol, m. p. 182—183° undepressed by admixture with that prepared from 2 : 4 : 6-trisacetoxymethylphenyl acetate.

Reaction of 2 : 4 : 6-*Trisacetoxymethylphenol with* p-*Cresol*.—2 : 4 : 6-Tri-(2-hydroxy-5-methylbenzyl)phenol was prepared by heating a mixture of 2 : 4 : 6-trisacetoxymethylphenyl acetate (10 g.) with *p*-cresol (250 g.) and concentrated hydrochloric acid (10 c.c.) on a water-bath for 6 hr. The product (10 g.) obtained by neutralisation with sodium carbonate and removal of excess of cresol in steam, followed by crystallisation from toluene, had m. p. 179—182°. On recrystallisation this furnished 2 : 4 : 6-tri-(2-hydroxy-5-methylbenzyl)phenol in prisms, m. p. 182·5—184·5° [Found: C, 79·1; H, 6·6%; *M* (micro-Rast), 423. Calc. for $C_{30}H_{30}O_4$: C, 79·3; H, 6·6%; *M*, 454]. In an experiment in which 2 : 4 : 6-trisacetoxymethylphenyl acetate (3·9 g.) was heated with *p*-cresol (100 g.) in the presence of toluene-*p*-sulphonic acid (0·15 g.) and the excess of cresol was removed in steam, white flakes (0·1 g.; m. p. 156—158°) later collected in the condenser. After recrystallisation from benzene–light petroleum these had m. p. 165·5—167° undepressed on admixture with 2 : 7-dimethylxanthen [Found: C, 85·1; H, 6·6%; *M* (micro-Rast), 212. Calc. for $C_{15}H_{14}O$: C, 85·7; H, 6·7%; *M*, 210]. In two further similar experiments the residues remaining after removal of *p*-cresol were substantially greater than that required for simple condensation. On evaporative high-vacuum distillation (150—190°/10^{-4} mm.) these furnished yields upwards of 20% (calc. on weight of residue) of 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane which after recrystallisation from benzene–light petroleum had m. p. and mixed m. p. 124—125°.

Reaction of 2 : 4 : 6-*Tri*-(2-*hydroxy*-5-*methylbenzyl*)*phenol with* p-*Cresol*.—(*a*) It was first ascertained that the tetranuclear Novolak was stable under the conditions of evaporative distillation: 0·1076 g. of a specimen whose m. p. had been raised to 186—187° by repeated recrystallisation was distilled at 10^{-4} mm. at a rate of 0·02 g. per hr. with a furnace temperature of 200—220°, and 0·1014 g. was recovered as a crystalline distillate, m. p. 189—191·5°, which did not depress the m. p. of the original specimen.

(*b*) 2 : 4 : 6-Tri-(2-hydroxy-5-methylbenzyl)phenol (1 g.), *p*-cresol (15 g.), and hydrochloric

acid (0·05 c.c.) were heated for 17 hr., *p*-cresol removed in steam, the residue extracted with ethyl acetate, and the material recovered from this subjected to evaporative distillation (3 hr. at 170—180°). The distillate, after recrystallisation from light petroleum and thereafter from aqueous acetic acid, furnished 2 : 4′-*dihydroxy-5-methyldiphenylmethane*, m. p. 133—135° which was undepressed by admixture with the specimen prepared from *p*-hydroxybenzyl alcohol and *p*-cresol (Found: C, 78·7; H, 6·8. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). In a similar experiment in which the tetranuclear Novolak (5 g.) was heated with *p*-cresol (75 g.) and hydrochloric acid (0·25 c.c.) for 17 hr., the distillate on recrystallisation from aqueous acetic acid and thereafter from light petroleum furnished 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenylmethane (0·05 g.), m. p. and mixed m. p. 125°. The mother-liquors furnished a small amount of 2 : 4′-dihydroxy-5-methyldiphenylmethane.

(*c*) A mixture of *p*-hydroxybenzyl alcohol (5 g.), *p*-cresol (50 g.), and toluene-*p*-sulphonic acid (0·1 g.) was heated on a water-bath overnight, then neutralised, and excess of cresol removed in steam. The product was distilled at 0·1 mm. (bath temp. 220—250°) and thereafter recrystallised from aqueous acetic acid, 2 : 4′-dihydroxy-5-methyldiphenylmethane being obtained (2·5 g.), m. p. 135—136° (Found: C, 78·1; H, 6·2%).

2 : 4 : 6-Tri-(2-hydroxy-5-methylbenzyl)phenol was prepared in 88% yield by heating 2 : 4 : 6-trishydroxymethylphenol (4 g.) with *p*-cresol (200 g.) and toluene-*p*-sulphonic acid (0·2 g.) on a water-bath for 4 hr. Excess of *p*-cresol was removed in steam after addition of 2 c.c. of 0·5N-sodium hydroxide. On recrystallisation from toluene 8·7 g. of the tetranuclear Novolak were obtained, having m. p. 180—182°. Further recrystallisation raised this m. p. to 183—184°.

2 : 4 : 6-*Tri-*(5-*bromo*-2-*hydroxybenzyl*)*phenol.*—(i) A mixture of 2 : 4 : 6-trisacetoxymethylphenyl acetate (1 g.), *p*-bromophenol (23 g.), and concentrated hydrochloric acid (1 c.c.) was heated on a water-bath for 5½ hr. After removal of excess of *p*-bromophenol in steam, the aqueous layer deposited crystalline material (0·25 g.), m. p. 192—194°, which on recrystallisation from ethylene dichloride–light petroleum furnished 2 : 4 : 6-*tri-*(5-*bromo*-2-*hydroxybenzyl*)*phenol* in small light pink crystals, m. p. 197—199° (Found: C, 49·5; H, 3·4; Br, 36·6. $C_{27}H_{21}O_4Br_3$ requires C, 49·9; H, 3·2; Br, 37·0%). No crystalline material could be isolated from the resinous residue obtained from distillation in steam. (ii) 2 : 4 : 6-Trishydroxymethylphenol (1 g.), *p*-bromophenol (10 g.), and hydrochloric acid (0·1 c.c.) were heated on a water-bath for 1½ hr., the excess of *p*-bromophenol was removed in steam, and the residue was extracted with benzene. On precipitation with light petroleum, 2 : 4 : 6-tri-(5-bromo-2-hydroxybenzyl)phenol was obtained (0·25 g.), having m. p. 195°, undepressed on admixture with the specimen previously obtained.

2 : 4 : 6-*Tri-*(4-*hydroxy*-3 : 5-*dimethylbenzyl*)*phenol*, prepared from 2 : 4 : 6-trisacetoxymethylphenyl acetate and 2 : 6 : 1-xylenol as for the 2′-hydroxy-3′ : 5′-dimethyl derivative, separated from toluene–light petroleum in deep yellow crystals, m. p. 168—170°. Repeated recrystallisation raised the m. p. to 177—179° but failed to free the substance from colour (Found: C, 80·4; H, 7·3%). By evaporative distillation (225—265°/10^{-4} mm.) the tetranuclear Novolak was obtained as an almost colourless crystalline deposit, m. p. 177—180° [Found: C, 80·2; H, 7·3; *M* (micro-Rast), 440. $C_{33}H_{36}O_4$ requires C, 79·8; H, 7·3%; *M*, 496].

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The Kinetics of the Reduction by Titanous Chloride of Azobenzene and 4-Aminoazobenzene.

By N. R. Large, F. J. Stubbs, and Sir Cyril Hinshelwood.

[Reprint Order No. 5211.]

The reduction of *trans*-azobenzene or of *trans*-4-aminoazobenzene by titanous chloride in aqueous-alcoholic solution is of the first order with respect to each component, the rate-determining step being the transfer of an electron from a titanous species to the azo-compound which has taken up protons. (The *cis*-compounds are reduced with very great rapidity and the *trans*-compounds must be freed from them for satisfactory measurements.) The 4-amino-compound yields aniline and *p*-phenylenediamine, but the unsubstituted azo-compound gives hydrazobenzene, 84% of which is very rapidly transformed into benzidine (or isomers), the remainder suffering reduction or disproportionation.

The most remarkable characteristic of the reductions is their dependence on the concentration of hydrochloric acid (Figs. 1 and 2) and of chloride ions, which follows a complicated power series, the curves becoming extremely steep at higher acid concentrations.

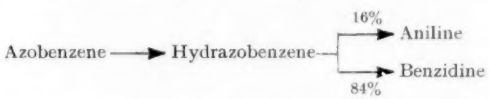
The simplest interpretation is that at higher acid concentrations the electrons from the titanous chloride are transferred to species of the type $PhNH\overset{+}{\cdot}\overset{+}{\cdot}NHPh$, the formation of which is facilitated by the screening action of oppositely charged chloride ions. The active titanous species appears to be a partially hydrolysed form, the concentration of which varies as an inverse power of the acid concentration.

Analogous assumptions about proton addition to azo- or hydrazo-compounds are useful in explaining the benzidine transformation and the disproportionation or reduction reactions (schemes I, II, III, p. 2743).

This work continues the general study of the kinetics of reduction by titanous chloride begun by Newton, Stubbs, and Hinshelwood (*J.*, 1953, 3384) with nitrobenzene and its substitution products. The kinetics of the reactions of titanous chloride with azobenzene, and with 4-aminoazobenzene have now been examined.

At the outset a complication appeared in that normally purified specimens of azobenzene showed an initial burst of very rapid reduction followed by a much slower reaction. This was traced to the fact that the *cis*-azobenzene present in most preparations is reduced very many times more rapidly than the predominant *trans*-form. Nearly pure *trans*-azobenzene was then prepared by Hartley's method (*J.*, 1938, 633) and used with precautions against its conversion into the *cis*-form by light. The small residual amounts of the *cis*-form, if present, were allowed for by a change in the origin of the reaction–time curves to a point beyond the initial rapid stage.

The stoicheiometry of the reaction indicated that only 16% of the azobenzene was reduced to aniline, the remainder being converted into benzidine (or isomers) by the isomerization of the hydrazobenzene, thus, formally:



The proportion of aniline was nearly independent of the titanous chloride concentration over a considerable range, and its formation was probably not by a direct action of titanous chloride on hydrazobenzene, as will be shown below.

When stoicheiometrically equivalent concentrations of azobenzene (in aqueous alcohol) and titanous chloride were employed the reaction–time curves followed the usual equation of the second order throughout their course, and separate variation of the concentrations

showed the rate to be proportional to the azobenzene and the titanous concentrations severally. It appears therefore that the rate-determining step is the primary attack of the titanous species on the azobenzene.

With the 4-amino-derivative of azobenzene the results were generally similar except that the reduction proceeded completely to the corresponding substituted aniline.

One of the most interesting aspects of the kinetics is the influence of acid concentration (which is shown in Figs. 1 and 2). With nitrobenzene the reduction rate had been found to be approximately proportional to the inverse square of the acid concentration, an effect explained by the variation in the concentration of the partially hydrolysed titanous complex assumed to be the active species. A rather similar influence is observable with the 4-aminoazo-compound in the lower acid range, but in the higher acid range the inverse dependence gives place to a very remarkable increase in rate with the concentration. A very similar increase is found with the azobenzene itself, while in the lower range the rate becomes nearly constant. This constancy, however, is seen by comparison of the results for nitrobenzene with those for 4-aminoazobenzene to be almost certainly due to a compensation of two opposing effects. In the lower acid range the rate falls because of a change

FIG. 1. *Effect of acid concentration on the rate of reduction of azobenzine at 25°.*

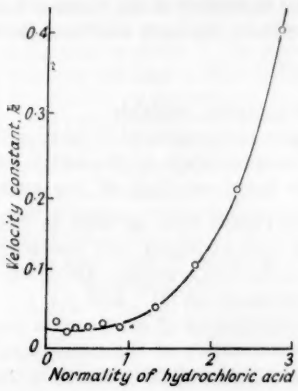
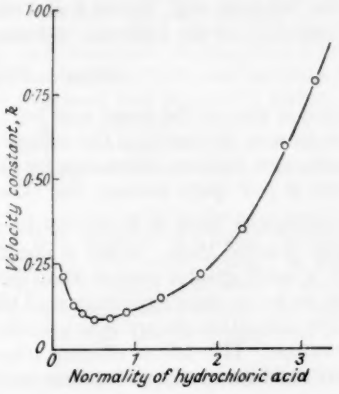


FIG. 2. *Effect of acid concentration on the rate of reduction of 4-aminoazobenzene at 25°.*



in the concentration of the active titanous species, while in the higher ranges it rises (in the case of the azo-compounds only, but not of nitrobenzene) in proportion to a high and increasing power of the concentration of hydrochloric acid.

The proportion of benzidine formed is nearly independent of the acid concentration. Thus the rate of isomerization of the hydrazobenzene, and the rate of formation of aniline, seem to follow similar laws. Carlin, Nelb, and Odioso (*J. Amer. Chem. Soc.*, 1951, **73**, 1002) state that the rate of the benzidine transformation is proportional to $[H^+]^2$, a law which, over a limited range, would agree with what has been found in the present experiments for the rate-determining step in the reduction of azobenzene. All these effects are rather unexpected.

When the rate is found to vary with the analytical concentration of hydrochloric acid this could indicate proportionality to $[H^+]\,[Cl^-]$ as much as to $[H^+]^2$, and in certain ranges added chloride ions were in fact found to have nearly as great an influence as hydrogen ions in accelerating the reduction of the azo-compounds.

It is significant that the dependence on a high power of the hydrochloric acid concentration seems to be characteristic of the binuclear bodies and of reactions where the simultaneous addition of two protons may be necessary for effective completion of the change. Azobenzene needs two protons (and two electrons from the reducing agent) for conversion into hydrazobenzene. The transformation of hydrazobenzene into benzidine formally requires none, but considerations of reaction entropy render it almost impossible that the

two protons appearing in the amino-groups should be the two which leave the *para*-positions. Thus here also the addition from the medium of two protons appears to be necessary (though no completion of the process by electrons from the reducing agent is required).

The addition of two protons to the same molecule cannot be expected to be easy, but will be much facilitated if the added ions are screened by ions of the opposite sign. Such screening can take place in various ways. Two H^+Cl^- ion pairs at the distance of the two reaction centres will repel one another less than two H^+ ions. Two quadrupoles, $\begin{pmatrix} H^+Cl^- \\ Cl^-H^+ \end{pmatrix}$, will do so even less, though the occurrence of the more highly screened structures becomes less and less probable. To a very rough approximation the probability of simultaneous addition might be set proportional to $a[H^+]^2 + b\{[H^+][Cl^-]\}^2 + c\{[H^+][Cl^-]\}^4$ or, if C is the analytical concentration of hydrochloric acid, to $\alpha C^2 + \beta C^4 + \gamma C^8$. The inaccuracy of each individual term of this expression will hardly be likely to invalidate the result that the rate is proportional to a series of increasing powers of C, as indeed appears to be found. (If in the benzidine transformation *para*-hydrogen atoms have to be removed as protons before the internal electron shifts permit the two nuclei to join—as a model shows they may—the negative ions may well have an additional function as receptors.)

The dependence of reduction rate on acid concentration is further complicated by the inverse proportionality of the more active titanous species to a power of the acid concentration (Newton *et al.*, *loc. cit.*), and this accounts for the flattening of the curve at low acid concentration or the existence of a minimum. The complete equation will be of the form :

$$\text{Rate} = C^{-n}(\alpha C^2 + \beta C^4 + \gamma C^8 \ldots) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where n in part of the range may be 2 or 3, but is itself probably variable.

In view of the fact that the influence of acid on the rate is represented by so complicated a series, and that the allowance for the change in the concentration of the active titanous species is not quite certain, the possibility cannot be ruled out that at the lower acid concentrations there is a contribution from the species $PhNH{:}\overset{+}{N}Ph$ as well as from the doubly charged form. What is important, however, is that at higher acid concentrations there is a still greater contribution from the species with the two protons. Otherwise there seems to be no clear explanation of the very steep dependence on $[H^+]$ and $[Cl^-]$.

The activation energy is independent of the acid concentration at least over a considerable range. This fact is of some importance in the consideration of the conditions under which valid comparisons between azobenzene and substituted derivatives can be made.

Experimental

Methods.—The solvent was a mixture of equal volumes of ethyl alcohol and water (42·5% of alcohol by weight).

The small amounts of the *cis*-isomers present in the azo-compounds were removed by Hartley's method (*loc. cit.*) and the purified compounds were stored in the dark to prevent isomerisation. A sample of *cis*-azobenzene prepared by Hartley and kindly given by Imperial Chemical Industries Limited, Dyestuffs Division, was used in some of the preliminary experiments. The azo-compounds were dissolved in absolute alcohol, and the titanous chloride in aqueous hydrochloric acid. In the calculation of the initial concentration of the reactants corrections were made for the contraction on mixing. The acid concentration of the titanous solutions was determined by potentiometric titration.

The course of the reaction was followed by determination of the residual azo-compound. Samples were pipetted into an excess of ferric alum solution and examined in a " Unicam " SP 600 Spectrophotometer at 440 mμ (for azobenzene) or 500 mμ (for 4-aminoazobenzene), calibration curves being prepared for each set of experimental conditions. End-points were determined by titration of the excess of ferric alum with titanous chloride.

All reaction flasks were blackened as a precaution against the isomerisation of the azo-compound by light, and were kept filled with carbon dioxide from a cylinder. Pipettes were flushed out with carbon dioxide before use.

The concentration of benzidine in the products was determined by addition of 5 ml. of the reaction mixture (from which the excess of titanous chloride had been removed by atmospheric

oxidation) to 5 ml. of 0·1M-potassium chlorate and 10 ml. of 0·012N-titanous chloride. An orange-red colour developed and reached a maximum intensity in about 15 min., after which the absorption at 550 mμ was measured in the spectrophotometer. Calibration curves were prepared with solutions of benzidine under the experimental conditions.

End-points.—Determination of end-points indicated that the amount of titanous chloride consumed was 116% of that required for the formation of hydrazobenzene (2·32 and 2·33 equiv. of $TiCl_3$ per mole of azobenzene in two experiments). The concentration of benzidine in the reaction products accounted for approx. 84% of the hydrazobenzene (83·6, 84·4, and 83·5% in direct benzidine determinations) and hence it was concluded that the remaining 16% was reduced to aniline. As a result of this preliminary investigation the experimentally determined equivalent concentrations of the reagents were used in later experiments. With 4-aminoazobenzene the consumption of titanous chloride corresponded to complete reduction of the azo-compound to the corresponding amine (3·96 and 4·09 equiv. of $TiCl_3$ per mole of 4-aminoazobenzene in two experiments, the theoretical amount being 4·0 equiv.).

Behaviour of the cis-*Isomer.*—In the early experiments in which a sample of azobenzene recrystallised from alcohol was used, a very rapid initial reaction was observed. Experiments on *cis*-azobenzene showed that the rate of reduction was very great and it was concluded that the anomalous reaction–time curves observed with ordinary azobenzene were due to the *cis*-azobenzene present in the recrystallised sample.

Methods of determining Velocity Constants.—Nearly pure *trans*-azobenzene was prepared and appeared to contain only a trace of the *cis*-isomer, but even this, owing to the very great difference in the rates of reduction of the isomers, had an appreciable effect on the reaction–time curve in the first moments. The remaining trace of the *cis*-isomer could be removed by mixing the azobenzene solution with a fairly concentrated hydrochloric acid solution for some time before the start of an experiment, and when this initial treatment was practicable satisfactory second-order rate constants were found. Where, however, a low acid concentration was needed in the experiment this procedure was impossible. In these cases satisfactory rate constants were obtained by displacement of the origin of the reaction–time curves to a point beyond the initial very rapidly-curving section.

In most experiments for the determination of velocity constants analytically equivalent concentrations of titanous chloride and azobenzene were used, 2·32 moles of $TiCl_3$ being known to be required for one mole of azobenzene. Thus $dx/dt = k(a - x)(b - 2{\cdot}32x)$ where b is usually $2{\cdot}32a$, so that $dx/dt = 2{\cdot}32k(a - x)^2 = k'(a - x)^2$. It should be noted that what is recorded in the Tables is in fact k, the true velocity constant of the initial rate-determining step, in sec.$^{-1}$ l. mole^{-1}. In the case of 4-aminoazobenzene b is usually $4{\cdot}0a$ since complete reduction to the amines occurs.

Order of Reaction.—The variation of the rate of reduction with the concentrations of titanous chloride and of azobenzene was determined from the initial rates which in each case were found to be proportional to the separate concentrations (Table 1).

TABLE 1. *Reduction of azobenzene : order of reaction.*

Rate is in mole of azobenzene consumed per l. per sec. [HCl] = 0·515N. 25·0°.

[$TiCl_3$], mole/l.	0·0062	0·0062	0·0062	0·0046	0·0031	0·00155	0·0031
[PhN:NPh], mole/l.	0·0031	0·0023	0·00155	0·0031	0·0031	0·0031	0·00155
$10^7 \times$ Rate	9·3	7·2	5·0	7·0	4·8	2·3	2·5
Rate/[$TiCl_3$][PhN:NPh]	0·048	0·050	0·052	0·049	0·050	0·048	0·052

At high acid concentrations the curve of a second-order reaction was obtained provided that the acid and the azo-compound were mixed for some time before the start of the experiment. Typical second-order rate constants are shown in Table 2.

TABLE 2. *Velocity constants at high acid concentrations.*

[$TiCl_3$] = 0·0031 mole/l. [PhN:NPh] = 0·00133 mole/l. [HCl] = 2·310N.

$10^4 \times$ Azobenzene consumed (mole/l.) ...	1·0	2·0	3·0	4·0	5·0	6·0	7·0	8·0	9·0
$10k$ at 20·0°	1·25	1·27	1·23	1·20	1·16	1·13	1·11	1·09	1·12
$10k$ at 40·0°	6·84	6·19	6·08	6·09	6·25	6·32	6·52	6·65	6·89

[$TiCl_3$] = 0·0031 mole/l. [4-Aminoazobenzene] = 0·000773 mole/l. [HCl] = 2·310N.

$10^4 \times$ 4-Aminoazobenzene consumed (mole/l.)	1·0	2·0	3·0	4·0	5·0
$10k$ at 10·0°	1·29	1·20	1·14	1·13	1·25

Table 3 shows the rate constants obtained at low acid concentrations compared with those obtained by displacement of the origin of the reaction–time curve to eliminate the rapid initial reaction of the traces of the *cis*-form.

TABLE 3. *Velocity constants at low acid concentrations.*

$[TiCl_3] = 0{\cdot}0031$ mole/l. [PhN:NPh] = 0·00133 mole/l. [HCl] = 0·257N. 30·0°.

$10^4 \times$ Azobenzene consumed (mole/l.)	1·0	2·0	3·0	4·0	5·0	6·0	7·0
$100k$	8·26	4·86	4·06	3·67	3·52	3·53	3·66
$100k$ *	—	3·60	3·39	3·25	3·22	3·31	3·51

$[TiCl_3] = 0{\cdot}0031$ mole/l. [4-Aminoazobenzene] = 0·000773 mole/l. [HCl] = 0·257N. 20·0°.

$10^4 \times$ 4-Aminoazobenzene consumed (mole/l.)	1·0	2·0	3·0	4·0	5·0
$100k$	14·3	11·0	9·31	8·69	8·97
$100k$ *	—	9·39	8·42	8·18	8·72

* Origin changed to "azobenzene consumed = $1{\cdot}0 \times 10^{-4}$ mole/l."

With 4-aminoazobenzene the order of reaction was verified by determination of rate constants for varying initial concentrations, as shown in Table 4.

TABLE 4. *Reduction of 4-aminoazobenzene: order of reaction.*

[HCl] = 2·310N. 25·0°.

$10^3[TiCl_3]$ (mole/l.)	3·1	1·55	3·1
10^4[4-Aminoazobenzene] (mole/l.)	7·73	7·73	3·86
k	0·355	0·42	0·36

Effect of Acid Concentration.—The effect of acid concentration on the reaction rate was investigated over a wide range. Fig. 1 shows the results obtained with azobenzene. At low acid concentrations the rate is nearly constant, but above 0·8N the curve closely follows a law which is not far from exponential in form. The curve obtained with 4-aminoazobenzene (Fig. 2) is closely similar at the higher acid concentrations, but at lower acid concentrations shows a well-defined minimum.

Salt Effects.—The effect of added chloride on the reaction rate is shown in Table 5 and also the effect of replacing some of the chloride ions by sulphate ions. The effect of chloride ions appears to be approximately the same as that of an equal concentration of hydrogen ions, while sulphate (or bisulphate) ions retard the reaction slightly.

TABLE 5. *Effect of chloride and sulphate ions.*

	Azobenzene				4-Aminobenzene		
$[H_2SO_4]$	—	—	2·053	2·053	2·053	—	—
[HCl]	2·310	0·826	0·257	0·257	0·257	2·291	2·256
[NaCl]	0·400	—	—	0·400	—	—	—
$[NH_4Cl]$	—	1·000	—	—	—	0·500	—
$[NH_4{\cdot}HSO_4]$	—	—	—	—	—	—	1·000
$[H^+]$	2·310	0·826	1·298	1·298	1·298	2·291	2·260
$[Cl^-]$	2·710	1·826	0·257	0·657	0·257	2·791	2·256
$([H^+] + [Cl^-])/2$	2·51	1·33	0·78	1·11	0·78	2·54	2·26
k (experimental)	0·264	0·057	0·026	0·029	0·115	0·49	0·30
k *	0·261	0·050	0·028	0·039	0·099	0·45	0·34

* k is the value of the rate constant for the hydrochloric acid concentration x, where $x = ([H^+] + [Cl^-])/2$ (Figs. 1 and 2).

Ionic concentrations are the nominal values corresponding to complete dissociation.

Activation Energy.—The activation energies for the reduction of azobenzene and of 4-aminoazobenzene respectively were each measured at two different values of the acid concentration, of which they were found to be almost independent. The activation energy is considerably lower for the amino-derivative than for azobenzene itself (Table 6.)

TABLE 6. *Activation energies.*

Temp. (°c)	[HCl]	Values of $100k$ 5·0°	10·0°	15·0°	20·0°	25·0°	30·0°	35·0°	40·0°	Activation energy (kcal./mole)
Azobenzene	0·257N	—	—	0·901	1·54	2·05	3·41	5·62	8·44	16·0
	2·310N	2·84	4·48	7·80	11·8	17·2	29·0	48·7	65·1	15·7
4-Aminoazobenzene	0·257N	—	4·0	6·95	8·65	10·9	18·0	23·7	38·7	12·6
	2·310N	—	11·9	19·1	25·1	35·5	49·8	81·7	—	12·7

Hydrazobenzene.—The hydrazo-compound appears to be the primary product of the reduction and the final products from azobenzene are aniline, benzidine, and isomers of benzidine. The behaviour of hydrazobenzene itself was therefore investigated, the amount of benzidine formed being estimated by the method described above, the probable amount of aniline formed being calculated from the concentration of the residual titanous chloride. In the absence of titanous chloride, hydrazobenzene when treated with acid yields a small quantity of azobenzene, the concentration of which could be estimated colorimetrically. The results of these experiments are shown in Table 7.

TABLE 7. *Products from hydrazobenzene.*

Compn. of reaction mixture.			Percentage of hydrazobenzene converted into		
[HCl](N)	10^4[Hydrazobenzene] (mole/l.)	10^3[$TiCl_3$] (mole/l.)	benzidine	aniline	azobenzene
2·310	7·7	—	79·1	—	5·2
0·905	7·7	—	79·3	—	5·3
0·257	7·7	—	84·1	—	7·3
2·310	7·7	3·09	87·2	16·7	—
0·905	7·7	3·09	89·5	19·8	—
0·257	7·7	3·09	93·8	19·8	—
2·310	3·8	—	84·0	—	8·2

Approximate estimates of the speed of the benzidine transformation under the experimental conditions showed it to be so rapid in comparison with the initial reduction of the azo-compound that its rate would not influence the kinetics of the reduction.

DISCUSSION

The reduction of *trans*-azobenzene (and of *trans*-4-aminoazobenzene) by titanous chloride is a reaction of the second order. The products from azobenzene are benzidine and aniline, the benzidine transformation being very much more rapid under the experimental conditions than the initial reduction to the hydrazo-compound, which is thus the rate-determining step.

The proportions of the products formed from hydrazobenzene itself are not much affected by the acid concentration, and thus it seems that the mechanisms by which aniline and benzidine are formed involve similar or identical intermediates. The proportion of benzidine is actually increased by the presence of titanous chloride, and this appears imcompatible with conversion of hydrazobenzene into aniline by direct reduction alone.

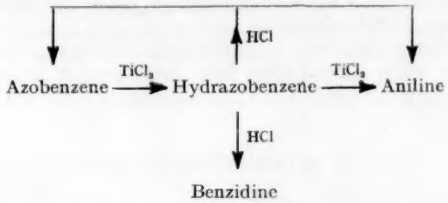
The disproportion of some of the hydrazobenzene into aniline and azobenene has been reported by Ingold and Kidd (*J.*, 1933, 984) and by Dewar (*J.*, 1946, 777), and this reaction is probably responsible for the formation of aniline in the present case. Given the percentage of benzidine formed in the absence of titanous chloride it should be possible to calculate the amounts of azobenzene and aniline produced and also the percentages of benzidine and aniline formed in its presence, when the azobenzene will be reduced again to hydrazobenzene. In Table 8 the experimentally determined values from Table 7 are compared

TABLE 8. *Products from hydrazobenzene; comparison of observed and calculated values.*

Percentage of hydrazobenzene converted into					
Benzidine		Aniline		Azobenzene	
obs.	calc.	obs.	calc.	obs.	calc.
79·1	—	—	—	5·2	10·4
79·3	—	—	—	5·3	10·3
84·1	—	—	—	7·3	7·9
87·2	88·3	16·7	12·8	—	—
89·5	88·5	19·8	10·5	—	—
93·8	91·4	19·8	6·2	—	—
84·0	—	—	—	8·2	8·0

with the calculated values, and good agreement is obtained for the benzidine formation, but for aniline and azobenzene the comparison is less satisfactory. This may be due in some measure to the difficulty in determining the residual titanous chloride with sufficient accuracy, but the low values of observed azobenzene formation tend to suggest other pos-

sible reactions. The disproportionation reaction and a direct reduction may both play some part in the formation of aniline, according to the scheme :



Uncertainty about the exact fate of the hydrazobenzene does not, however, affect the main conclusion, namely, that the rate-determining step is the reduction of the azo-compound to the hydrazo-compound, or vitiate measurements of the rate of this reaction.

With 4-aminoazobenzene, there is no evidence of a benzidine change, the final products being aniline and *p*-phenylenediamine. The absence of a benzidine derivative may be attributed to the blocking effect of the *para*-substituent, the product formed being a semidine which is further reduced to the primary amines.

The acid concentration has little effect on the activation energy, but a remarkable one on the rate (Figs. 1 and 2). A rapid increase in the order of reaction with respect to acid concentration is found at concentrations above about 0·8N. A comparable effect is produced by chloride ions, but sulphate or bisulphate ions simply cause a slight retardation.

These effects are in marked contrast with what is found in the reduction of nitrobenzene, where the rate over a certain range is inversely proportional to the square of the acid concentration, and only slightly affected by chloride ions (Newton *et al.*, *loc. cit.*). The reduction of azoxybenzene in these respects resembles that of nitrobenzene (M. J. Stephen, unpublished work). The inverse relationship is almost certainly a function of the titanous species, and the rapid increase in order at higher acid concentrations in the present case is a function of the azobenzene species.

The more or less exponential increase in rate suggests that the relationship may be in fact a power series of the general form suggested by equation (1), an interpretation of which has already been discussed. With azobenzene a logarithmic plot of the results in Fig. 1 indicated that the power of the acid concentration to which the rate is proportional rises from zero to roughly 7 in the range 0·5N to 3·5N. With 4-aminoazobenzene the course is generally similar.

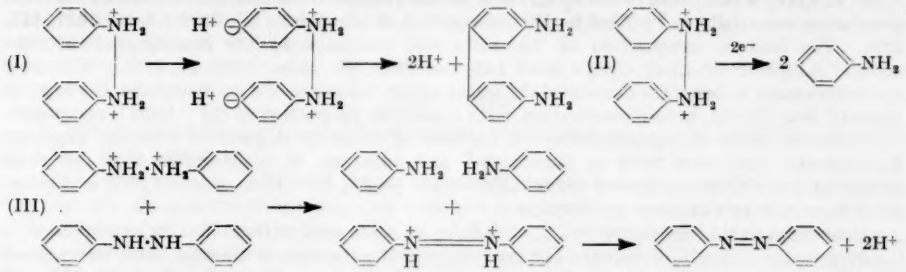
The earlier investigations with nitrobenzene did not include the high acid concentrations used in the present work, so that no very accurate estimate of the way in which the active titanous species varies can be made. Apart from this, more than one such species may participate, and the complicated interionic effects cannot be allowed for quantitatively. For this reason it is hard to say whether at lower acid concentrations $PhN\overset{+}{H}{:}NPh$ is a reactive species or not. But there seems little doubt about the increasing importance of $PhN\overset{+}{H}{:}\overset{+}{N}HPh$ over most of the range in Fig. 1.

In the lower acid range there is a difference in behaviour between azobenzene and its amino-derivative which follows a relation similar to that found with nitrobenzene. The apparent independence of acid concentration found with azobenzene in this same range must be due to the compensating variations of concentration of the reactive species ($PhN\overset{+}{H}{:}\overset{+}{N}HPh$) on the one hand and of the active titanous species on the other. In acid solution the 4-amino-compound must exist mainly in the form $PhN{:}N{\cdot}C_6H_4{\cdot}\overset{+}{N}H_3$, and since the positive charge reduces the probability of addition of two further protons to the azo-group, the dependence on acid concentration is shifted relatively to that of azobenzene. Over the lower acid range the predominating influence is now that of the variation of the concentration of the active titanous species, which is known from the work on nitrobenzene to depend upon $[HCl]^{-2}$ or $[HCl]^{-3}$.

It seems therefore that one of the most important reacting species in the reduction of

the azo-compounds is the one with the two positive charges on the azo-group (suitably screened), $PhN\overset{+}{H}:\overset{+}{N}HPh$, to which, in the rate-determining step, an electron is transferred from the titanous species. This step will be followed by the rapid transfer of a second electron from the reducing agent.

This view that the electron transfer is in fact the rate-determining step is consistent with the fact that the activation energy for 4-aminoazobenzene is lower than that for azobenzene itself, the positive charge conferred on the molecule by the $\cdot\overset{+}{N}H_3$ group facilitating the transfer. (The substituent influences are being further investigated.)



As suggested earlier, the law found by Carlin, Nelb, and Odioso (*loc. cit.*) for the effect of acid on the rate of the benzidine transformation may probably be regarded as similar to that found in the present work for the reduction of the azo-compounds. Moreover, the relative amounts of benzidine and of aniline formed from azobenzene are nearly independent of the acid concentration. There is thus the interesting possibility that the participation of a common intermediate explains all these observations, the various reactions being formulated according to the annexed scheme.

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The Hydrogen Isotope Effect in the Metallation of Benzene and Toluene.

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In the metallation of deuterobenzene and α-deuterotoluene by ethylpotassium, protium is replaced by potassium more rapidly than is deuterium. The respective rate ratios, k_D/k_H, are $0{\cdot}50 \pm 0{\cdot}10$ and $0{\cdot}22 \pm 0{\cdot}05$. Part, but probably not all, of the difference between the ratios may be attributed to the use of a higher temperature for the former reaction. The observed selectivity supports the " protophilic " mechanism for metallation reactions of this type (Bryce-Smith, *J.*, 1954, 1079).

WHENEVER the breaking of the bond attached to a hydrogen atom plays a part in determining the rate of its replacement, the velocity is expected to be greater when that hydrogen atom is one of protium, than when it is one of deuterium. The rate of replacement of deuterium (k_D) divided by that of protium (k_H) is known as the isotopic rate ratio for the particular reaction.

When a compound containing a known distribution of the two isotopes among its molecules is attacked by a deficit of a substituting reagent, determination of the deuterium abundance of the product enables the value of k_D/k_H to be calculated, as is shown below.

These considerations have been the basis of the present work, the aim of which has been to test the validity of the protophilic mechanism for aromatic metallation, evidence for which has recently been advanced by one of us (Bryce-Smith, *loc. cit.*).

Both side-chain and nuclear metallation have been studied by means of the following reaction (Bryce-Smith, *loc. cit.*; Bryce-Smith and Turner, *J.*, 1953, 861):

(1) $PhH + EtK = PhK + C_2H_6$; $PhK + CO_2 \longrightarrow Ph{\cdot}CO_2K$

(2) $PhMe + EtK \longrightarrow Ph{\cdot}CH_2K + C_2H_6$; $Ph{\cdot}CH_2K + CO_2 \longrightarrow Ph{\cdot}CH_2{\cdot}CO_2K$

Experimental

Isotope Analysis.—A sample of organic compound, sufficient to provide about 0·35 ml. of water, was burnt according to standard semimicro-procedure. The water was condensed, at −80°, in a trap which could be sealed off from the combustion train. It was purified by repeated distillation essentially as by Keston, Rittenberg, and Schoenheimer (*J. Biol. Chem.*, 1937, **122**, 227). The isotopic composition of the water was measured by the density-gradient tube method (Linderstrøm-Lang, *Compt. rend. Lab. Carlsberg, Sér. chim.*, 1936, **21**, 315). Whenever it was necessary to bring the density of the water within the range of a gradient tube, the original material was diluted, before combustion, with a suitable proportion of the "light" compound.

From the level of reproducibility of analyses at different degrees of dilution, duplicate experiments, and other tests of "memory" and accuracy, it is estimated that the atom percentages of deuterium quoted are reliable within ±0·1% for values of about 20% and somewhat more accurate at lower percentages.

Deuterium oxide, containing 99·7% of D_2O by wt., was used in the following experiments.

Preparation of [α-$^2H_1$]*Toluene.*—The product from the reaction of ethereal benzylmagnesium chloride with deuterium oxide (cf. Choppin and Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 577) was treated with solid carbon dioxide to destroy excess of the Grignard reagent. Crude deuterotoluene, b. p. 110°, was obtained in 60% yield by fractional distillation, contact with mineral acids being avoided in order to run no risk of isotope exchange (Found: D, 11·72. Calc. for C_7H_7D: D, 12·50 atoms %). A portion of the product was oxidised by alkaline permanganate. The resulting benzoic acid contained D, 0·20 atom %. This indicated the presence of nuclear deuterium in the toluene, but it is uncertain whether this arose from a rearrangement during the hydrolysis (cf. Coleman and Forrester, *ibid.*, 1936, **58**, 27) or from the presence of nuclear isomers in the specimen of benzyl chloride which was used (cf. Melander, *Arkiv Kemi*, 1950, **2**, 261). Turkevich, McKenzie, Friedman, and Sporr (*J. Amer. Chem. Soc.*, 1949, **71**, 4045) showed that no dideuterium compounds are formed in the reaction concerned. Accordingly the present product had the following composition: C_7H_8, 6·2; $C_6H_4D{\cdot}CH_3$, 1·2; $C_6H_5{\cdot}CH_2D$, 92·6 mole %.

Preparation of Deuterobenzene ([$^2H_1$]*Benzene*).—The Grignard procedure described by Weldon and Wilson (*J.*, 1946, 235) was modified in order to avoid working with solvent-free phenylmagnesium bromide. A solution of phenylmagnesium bromide was prepared by the addition (30 min., stirring) of a solution of bromobenzene (125 g., 0·8 mole) in di-*n*-butyl ether (200 ml., dry, peroxide-free) to a heated suspension of magnesium (20 g., 0·82 g.-atom) in the same solvent (50 ml.) under anhydrous conditions. Reaction commenced almost immediately at 140° and stirring was continued at this temperature (15 min.). Material of b. p. <149° was removed at once by distillation through a 20-cm. Fenske column, *ca.* 15 ml. of benzene being obtained. Deuterium oxide (16·4 g., 0·82 mole) was added (2 hr., stirring) to the solution at 60° and after the mixture had been kept overnight at room temperature, crude deuterobenzene (29·5 g.) was obtained by distillation through the column. Further fractional distillation, followed by fractional freezing, gave a product of m. p. 5·5° (22·5 g.) (Found: D, 15·30. Calc. for C_6H_5D: D, 16·67 atoms %). On the assumption (cf. Weldon and Wilson, *loc. cit.*) that molecules containing more than one deuterium atom were absent, the composition of the material (benzene A) was: C_6H_6, 8·0; C_6H_5D, 92·0 mole %.

Mixed Deuterobenzenes ([^2H]*Benzene*).—The method of Ingold, Raisin, and Wilson (*J.*, 1936, 915) was used. Benzene (90 ml.) was shaken at room temperature for 150 hr. with deuterosulphuric acid (18 g.) which was stronger than monohydrate. Exchange equilibrium should have been reached under these conditions. Analysis of the product gave *D*, 7·8 atoms %. On the assumption that the distribution of deuterium atoms is random, the material (benzene B) had the following composition: C_6H_6, 62·8; C_6H_5D, 29·2; $C_6H_4D_2$, 6·8; $C_6H_3D_3$, 1·06; $C_6H_2D_4$, 0·13; C_6HD_5, 0·01 moles %. C_6D_6, negligible.

Metallation Experiments.—The general procedure described by Bryce-Smith and Turner (*loc. cit.*) was used.

(a) *Benzene.* A solution of ethyl-lithium (0·43 mole) in the deuterobenzene (20 ml.) was stirred at 75° with potassium (3·5 g., 0·09 g.-atom) until gas evolution had become negligible

(2·5 hr.). The dark brown product was cooled and poured on solid carbon dioxide in ether. Alkali metals were destroyed by the cautious addition of aqueous *tert.*-butyl alcohol. Dicarboxylic acids were removed from the product by virtue of their insolubility in chloroform. Benzoic acid (2·35 g.; m. p. 117—119°) was obtained by evaporation of the chloroform. After recrystallisation from water it melted at 121·5°. The acid obtained by metallation of benzene A was found to contain 13·8 atoms % of deuterium and that from benzene B to contain 6·41 atoms %.

(b) *Toluene.* An alloy of potassium (5 g.) and sodium (1 g.) was added to the stable solution of ethyl-lithium (0·07 mole) in the deuterotoluene (33 g.) at 20°. The mixture was stirred at this temperature until the evolution of gas had become negligible (125 hr.). Reaction with solid carbon dioxide in ether gave phenylacetic acid (m. p. 66°; 3·5 g.) which after a single recrystallisation from light petroleum (b. p. 40—80°) melted at 76·7°. This acid was found to contain 10·4 atoms % of deuterium.

Discussion

It is convenient to express the experimental results in terms of the isotopic rate ratios to which they correspond.

Calculation of k_D/k_H.—When a deficit of reagent is used, as in the experiments described, the isotopic abundance of the reaction product is a function, not only of k_D/k_H and the isotopic abundance of the starting material, but also of the distribution of the two isotopes among the molecules of the starting material. In the calculations it has been assumed that the amount of reagent consumed was negligible compared with the amount of benzene or toluene present, so that the isotopic composition of the hydrocarbon was effectively constant. The principle of the calculation for a mixture of isotopically different benzene molecules is as follows. If h and d are proportional to the reactivities of positions carrying protium and deuterium atoms respectively, *i.e.*, proportional to k_H and k_D, then n_0 molecules of C_6H_6 will yield $6hn_0$ molecules of $C_6H_5{\cdot}CO_2H$, while n_1 molecules of C_6H_5D yield $5hn_1$ molecules of $C_6H_4D{\cdot}CO_2H$ and dn_1 molecules of $C_6H_5{\cdot}CO_2H$, and n_2 molecules of $C_6H_4D_2$ yield $4hn_2$ molecules of $C_6H_3D_2{\cdot}CO_2H$ and $2dn_2$ molecules of $C_6H_4D{\cdot}CO_2H$, etc. In this way the known isotopic composition of the product may be obtained in terms of the known values of n_0, n_1, n_2, etc., for the starting material and of h and d. Hence d/h $(= k_D/k_H)$ may be calculated, or, reversing the calculation, the atom percentage of deuterium to be expected in the product can be found for a variety of assumed values for k_D/k_H.

Table 1. *Variation with* k_D/k_H *of the atom percentage of deuterium to be expected in the product.*

	Atom % expected in product		
k_D/k_H	Benzene A	Benzene B	Toluene
0·00	$15{\cdot}1_0$	6·36	$11{\cdot}3_9$
0·20	$14{\cdot}5_7$	—	$10{\cdot}4_6$
0·25	$14{\cdot}4_4$	—	$10{\cdot}2_4$
0·333	$14{\cdot}2_3$	—	$9{\cdot}9_0$
0·40	$14{\cdot}0_8$	—	$9{\cdot}7_0$
0·50	$13{\cdot}8_5$	6·41	$9{\cdot}3_1$
1·00	$12{\cdot}7_8$	6·47	$7{\cdot}8_7$

Found: Benzene A, 13·8 ± 0·09; Benzene B, 6·41 ± 0·03; Toluene, 10·4 ± 0·09 atom %.

Table 1 illustrates, in the case of benzene, the effect of altering the isotopic distribution in the starting material and shows that, on consideration of the experimental error, the identification of the rate ratio is more clear-cut when one species greatly predominates, the presence of others restricting the range of atom percentages that can be expected in the product. The experimental values indicate that for benzene $k_D/k_H = 0{\cdot}50 \pm 0{\cdot}10$ and that for toluene $k_D/k_H = 0{\cdot}22 \pm 0{\cdot}05$. In both cases, therefore, metallation involves a definite isotope effect. The isotopic rate ratios obtained are of the same order as those found by other workers for reactions involving hydrogen abstraction (see, *e.g.*, review by Bonhoeffer, *Trans. Faraday Soc.*, 1938, **34**, 252). Of particular interest also in relation to the present

work is that of Melander (*loc. cit.*; Berglund-Larsson and Melander, *Arkiv Kemi*, **1953**, **6**, 219) who has used tritium to study the mechanism of electrophilic aromatic substitution.

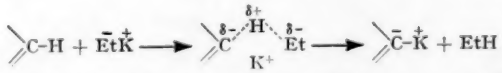
In general, correlations should exist between the measured value of k_D/k_H on the one hand, and the force constant of the broken bond, the strength of the accepting base, the temperature, and, to a smaller extent, the nature of the solvent, on the other. The first two items help to determine the important zero-point energy differences, and the temperature controls the magnitude of the factor arising from these differences and also that arising from the possible incidence of quantum-mechanical tunnelling. Finally the value of k_D/k_H will also depend upon the relative importance of the rôle which the breaking of the hydrogen linkage plays in determining the overall rate.

Work in this field up till now has not been systematic or precise enough to allow definite conclusions to be drawn about the relative importance of these various factors. At present, therefore, comparison of two isotopic rate ratios does not always afford unequivocal deductions.

In the present work, apart from the inevitable change in solvent and any difference between the force constants of side-chain and nuclear hydrogen bonds, the reaction with benzene was carried out, for reasons of experimental convenience, at a temperature 55° higher than that with toluene. If the isotopic rate ratio is attributed entirely to the difference in heat of activation occasioned by the differences in zero-point energy between isotopic compounds, then the differences in heats of activation corresponding to the observed ratios for benzene and for toluene are about 480 and 890 cals. respectively. The larger of these values is too small to account for the change in the ratio k_D/k_H from 0·22 to 0·50 for a rise in temperature of 55°. However, temperature effects of a greater magnitude than this have previously been reported for the ionisation of 2-*o*-carboxybenzylindan-1-one (Wilson, *J.*, 1936, 1550) where k_D/k_H changed from 0·23 to 0·33 for a rise in temperature of only 20°. Although Wilson did not consider his data to be incompatible with the sole operation of the zero-point energy effect on the activation energies, nevertheless, it seems possible that in his experiments and in the present work the quantum-mechanical tunnel effect is making itself felt, so that the two values, 0·50 and 0·22, need not in fact imply any fundamental difference between the two reactions.

However this may be, it is clear that the loss of hydrogen is of kinetic significance and, to be acceptable, any mechanism for metallation must account for this. The mechanism recently supported by one of us (Bryce-Smith, *loc. cit.*) passes the test.

Isomer ratios, partial rate factors, and other considerations in connection with the metallation of alkylbenzenes led to the following reaction scheme for the replacement of a nuclear hydrogen atom :



In the present case, that of potassium, the metal alkyl is considered to behave as an ion pair, any effect due to the metal being electrostatic. The reaction scheme for the other alkali metals is thought to be broadly similar, though not necessarily identical in all details. The same is probably true for side-chain in relation to nuclear substitution, both reactions being essentially protophilic in character. The hydrogen atom is accordingly removed as a proton and hence benzene, toluene, and other hydrocarbons to which the mechanism applies are logically described as acids in this reaction (Bryce-Smith, *loc. cit.*). Acidic behaviour in the methyl group of toluene is a concept which is not wholly foreign. It should be especially well developed if a nitro-group is also present in the ring as is shown by the base-catalysed condensation of nitrotoluenes with benzaldehyde. Toluene itself appears to behave as an acid in its reaction with cæsium, forming the salt benzylcæsium and evolving hydrogen (de Postis, *Compt. rend.*, 1946, **222**, 398). The suggestion that the nuclear hydrogen atoms of an aromatic compound can, in suitable circumstances, behave in an acidic fashion may, perhaps, not find ready acceptance. Here again, however, it is possible to strengthen their acidity with electron-withdrawing substituents and the acidity of the hydrogen atoms in trinitrobenzene is revealed by the observation that this compound

will undergo hydrogen-isotope exchange with ethanol only in the presence of alkali (Kharasch, Brown, and McNab, *J. Org. Chem.*, 1937, **2**, 36).

One of us (D. B.-S.) is in tenure of an I.C.I. Research Fellowship at the University of London.

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Homolytic Aromatic Substitution. Part VI. Lead Tetrabenzoate—a New Phenylating Agent.*

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Lead tetrabenzoate reacts with chlorobenzene and with nitrobenzene at 130° to give mixtures of the isomeric chlorodiphenyls and nitrodiphenyls respectively. The ratio of the isomers formed in the phenylation of nitrobenzene by lead tetrabenzoate is similar to that formed in the corresponding reaction with benzoyl peroxide. Lead tetrabenzoate effects the fission of vicinal glycols, whereas with benzoyl peroxide oxidation to ketonic products results. The mechanisms of these reactions are briefly discussed.

FIESER and CHANG (*J. Amer. Chem. Soc.*, 1942, **64**, 2043) have shown that salts of quadrivalent lead with aliphatic acids can act as alkylating agents for α-naphthaquinones. In this manner 2-methyl-1 : 4-naphthaquinone was converted by lead tetra-acetate into 2 : 3-dimethyl-1 : 4-naphthaquinone, with evolution of carbon dioxide, in yields as high as 50% by operating in boiling acetic acid or at lower temperatures in the presence of a promoter, such as malonic acid, ethyl acetoacetate, or methanol. Similar reactions could be effected by the use of red lead, a promoter, and the appropriate acid. The reaction was applied to the introduction of several alkyl groups, of the benzyl group, and of the phenethyl group. In a subsequent publication (Fieser, Clapp, and Daudt, *ibid.*, p. 2052) it was shown that lead tetra-acetate was also capable of effecting the methylation of aromatic nitrocompounds and the reaction with nitrobenzene gave a mixture of *o*- and *p*-nitrotoluene. Similar reactions with benzene and chlorobenzene gave benzyl and chlorobenzyl acetates by successive methylation and acetoxylation, whereas naphthalene gave only 1-acetoxynaphthalene. These workers recognised the general resemblance between these reactions and (*a*) the electrolytic decomposition of sodium acetate in the Kolbe synthesis and (*b*) the reactions of acetyl peroxide. The intervention of free methyl radicals was considered and the suggestion was made that lead tetra-acetate might break down into lead diacetate and acetyl peroxide. Such acyl peroxides were shown to be excellent reagents for the alkylation of quinones (Fieser and Oxford, *ibid.*, p. 2060). In spite of the known phenylating action of benzoyl peroxide (Gelissen and Hermans, *Ber.*, 1925, **58**, 285; Hey, *J.*, 1934, 1966; Hey and Walker, *J.*, 1948, 2213) no work appears to have been carried out on lead tetrabenzoate as a potential phenylating agent.

The acceptance of common mechanisms to account for the reactions of lead tetra-acetate and acetyl peroxide has been questioned by Kharasch, Friedlander, and Urry (*J. Org. Chem.*, 1951, **16**, 533), who pointed out that the decomposition of lead tetra-acetate is dependent upon the solvent present and that the products obtained with these two compounds are frequently not strictly comparable. In particular, the reaction of a vicinal glycol with lead tetra-acetate results in the cleavage of a carbon–carbon bond, whereas with acetyl peroxide oxidation takes place to give a hydroxy-ketone and a diketone (*idem, ibid.*, 1949, **14**, 91). A comparison of the reactions of (*a*) lead tetra-acetate and (*b*) acetyl peroxide with acetic acid and with *iso*propyl ether revealed marked differences in the nature and proportions of the products formed, and these were attributed to a fundamental difference in mechanism. Whereas acetyl peroxide appeared

* Part V, *J.*, 1954, 794.

to react by predissociation into free radicals, lead tetra-acetate was considered to undergo a bimolecular reaction with the solvent, and the logical consequences of these assumptions were shown to be consistent with the differences in product distribution observed in the two reactions. Both reactions, however, were considered to be of homolytic character.

The oxidation of vicinal glycols by lead tetra-acetate, however, is quite distinct and does not involve the liberation of either carbon dioxide or methane. It proceeds at relatively low temperatures and does not involve free radicals. It thus appears that there is adequate experimental evidence to indicate that the reactions of lead tetra-acetate can follow either a heterolytic or a homolytic course according to environmental circumstances (cf. Cordner and Pausacker, *J.*, 1953, 102; Mosher and Kehr, *J. Amer. Chem. Soc.*, 1953, **75**, 3172; Barron, Cavill, Cole, Gilham, and Solomon, *Chem. and Ind.*, 1954, 76). In the present communication the reactions of lead tetrabenzoate have been investigated with particular reference to some of the known reactions of benzoyl peroxide.

Lead tetrabenzoate was first prepared by Criegee (*Annalen*, 1930, **481**, 263), who reported its reaction with *cyclo*pentadiene at 35° to give the dibenzoate of *trans*-3-*cyclo*pentene-1 : 2-diol. Hurd and Austin (*J. Amer. Chem. Soc.*, 1931, **53**, 1543) modified Criegee's preparation; their product probably contained benzene of crystallisation and, on pyrolysis, gave a resinous mass from which lead dibenzoate and benzoic acid were separated. Elming and Clauson-Kaas (*Acta Chim. Scand.*, 1952, **6**, 535) have reported that furan and lead tetrabenzoate in benzene solution at 75° give 2 : 5-dibenzoyloxy-2 : 5-dihydrofuran. It is now shown that the decomposition of lead tetrabenzoate in chlorobenzene at 130° results in the formation of a mixture of isomeric chlorodiphenyls by nuclear phenylation. A similar reaction with nitrobenzene gave a mixture of isomeric nitrodiphenyls. In the former reaction the presence of 4-chlorodiphenyl in the product was proved by its conversion into 4-bromo-4'-chlorodiphenyl, and from the latter reaction both 2- and 4-nitrodiphenyl were isolated. Moreover, the exact composition of the mixture of nitrodiphenyls obtained from the reaction between lead tetrabenzoate and nitrobenzene was shown by means of ultra-violet spectrophotometry to be 55% *ortho*, 16% *meta*, and 29% *para*. A comparable reaction carried out under identical conditions with benzoyl peroxide in place of lead tetrabenzoate gave 56·3% *ortho*, 15·7% *meta*, and 28·0% *para*. The figures for the reaction with benzoyl peroxide now given refer to the reaction at 125° and the slightly different figures previously reported (Hey, Nechvatal and Robinson, *J.*, 1951, 2892), namely, 59·5% *ortho*, 10·0% *meta*, and 30·5% *para* (mean values), refer to the reaction carried out at 80°. It is thus clear that the phenylating action of lead tetrabenzoate follows closely the pattern observed with benzoyl peroxide and the various diazo-derivatives discussed by Hey, Nechvatal, and Robinson (*loc. cit.*). At 125° lead tetrabenzoate reacts by the liberation of benzoyloxy-radicals which by subsequent loss of carbon dioxide provide phenyl radicals.

On the other hand, a comparison of the reactions of lead tetrabenzoate and of benzoyl peroxide with butane-2 : 3-diol reveals the same contrast which is shown between lead tetra-acetate and acetyl peroxide (Kharasch, Friedlander, and Urry, *locc. cit.*). Butane-2 : 3-diol reacts rapidly with lead tetrabenzoate at 15° to give acetaldehyde in at least 78% yield. With benzoyl peroxide no reaction takes place in the cold, and at temperatures above 80° the product contains diacetyl and acetoin but no acetaldehyde. The glycol fission by both the tetra-acetate and the tetrabenzoate is a specific reaction which does not appear to involve free radicals (cf. Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159; Waters, in Gilman's " Organic Chemistry," Vol. IV, J. Wiley & Sons, N.Y., 1953, p. 1189) but the high-temperature reaction between a vicinal glycol and either acetyl or benzoyl peroxide shows the general features of a homolytic process. This interpretation of the reaction between benzoyl peroxide and a vicinal glycol is supported by the isolation of benzene, diphenyl, and diphenyl-4-carboxylic acid from the products of the reaction.

Experimental

Reagents.—Nitrobenzene (" AnalaR ") was washed with concentrated aqueous sodium hydroxide, then with water, and distilled with steam. After being dried ($CaCl_2$) it was fractionally frozen six times. Chlorobenzene was fractionally distilled from phosphoric oxide

and collected at 132°/760 mm. Butane-2 : 3-diol was fractionally distilled and collected at 86—90°/20 mm. (n_D^{20} 1·4363). Methylene chloride was dried (P_2O_5) and distilled before use.

Lead tetrabenzoate was prepared by a modification of Criegee's method (*loc. cit.*). Lead tetra-acetate (50 g.), prepared by Bailar's method (*Inorg. Synth.*, 1939, **1**, 47), was added with shaking to molten benzoic acid (60 g.) at 130°. When the addition was complete the liberated acetic acid was removed at 40 mm. The solid residue, when cold, was broken up and thoroughly extracted with sodium-dried ether to remove free benzoic acid. The dry product (80 g.), after three crystallisations from dry (P_2O_5) methylene chloride, melted at 185° with decomposition. This product contained methylene chloride which was removed by heating at 100° for 3 hr. at 0·01 mm. to give a solvent-free compound as a pale yellow amorphous powder, m. p. 176° (decomp.) (Criegee, *loc. cit.* reported m. p. 168°). A specimen, m. p. 185°, recrystallised from chlorobenzene, gave the following analysis: C, 51·55; H, 3·45; Cl, 5·3. [Calc. for $4Pb(O{\cdot}CO{\cdot}Ph)_4,5C_6H_5Cl$: C, 51·2; H, 3·2; Cl, 5·3%]. The product was stored in a desiccator over phosphoric oxide.

The purity of successive batches of lead tetrabenzoate was determined iodometrically as follows: to a solution of lead tetrabenzoate (*ca.* 0·3 g.) in acetic acid (25 c.c.) was added a volume of aqueous potassium iodide (containing 9·6 g. of KI, 50 g. of Na_2CO_3, and 45 g. of NaOAc per litre) such that the potassium iodide was equivalent to the weight of the tetrabenzoate taken, assumed to be 100% $Pb(O{\cdot}CO{\cdot}Ph)_4$. The iodine liberated, which corresponds to 2 atoms per mol. of lead tetrabenzoate, was titrated with 0·05N-thiosulphate. The validity of the method was checked by microanalytical estimations for carbon and hydrogen.

Decomposition of Lead Tetrabenzoate in Chlorobenzene.—Lead tetrabenzoate (17 g.), crystallised from and containing chlorobenzene (2·6 g.), was dissolved in warm chlorobenzene (150 g.), and the solution was boiled under reflux. The solution darkened and after 45 hr. the decomposition was complete as shown by a negative starch–iodide test. Lead benzoate was filtered off from the cold mixture, and free benzoic acid was extracted with aqueous saturated sodium hydrogen carbonate (3 × 75 c.c.). The mixture was then washed with water and dried ($CaCl_2$). Chlorobenzene was removed by distillation through a 25 cm. helix-packed column, and esters in the residue (15 ml.) were hydrolysed for 4 hr. with 100 c.c. of boiling ~2N-sodium hydroxide. The unsaponifiable material was thoroughly extracted with benzene, and the benzene extracts, after being dried ($CaCl_2$), were chromatographed on an alumina column (2 × 25 cm.) and eluted with the benzene washings of the calcium chloride (100 c.c.) and ether (100 c.c.). Ether and benzene were removed from the combined eluates by distillation through a 25 cm. helix-packed column, and subsequent distillation of the residue by the method described by Augood, Hey, and Williams (*J.*, 1952, 2094) gave a mixture of chlorodiphenyls as a colourless oil (1·8 g.), b. p. 60—94°/0·2 mm. (Found: C, 76·7; H, 5·1; Cl, 18·3. Calc. for $C_{12}H_9Cl$: C, 76·4; H, 4·8; Cl, 18·8%). Bromination with a solution of bromine in acetic acid at 100° gave 4-bromo-4′-chlorodiphenyl, m. p. and mixed m. p. 154—155° after crystallisation from alcohol (cf. Hey, *J.*, 1934, 1968).

Decomposition of Lead Tetrabenzoate in Nitrobenzene.—(i) *Qualitative.* Lead tetrabenzoate (17·3 g.) was added with vigorous stirring to nitrobenzene (220 c.c.) at 130°. The solution darkened rapidly and stirring was continued until all the tetrabenzoate had dissolved. Heating was continued at 130° until decomposition was complete. Lead dibenzoate did not separate from the cold mixture but was precipitated by the addition of water, and filtered off. Except that nitrobenzene was removed at reduced pressure (20 mm.), the working-up was the same as that described for the decomposition in chlorobenzene. The final distillation, as in the preceding example, gave a pale yellow oil (1·9 g.) which partly solidified, b. p. 95—100°/0·2 mm. (Found: C, 72·7; H, 4·8; N, 7·15. Calc. for $C_{12}H_9O_2N$: C, 72·5; H, 4·5; N, 7·0%). A portion of this product (1 g.) in light petroleum (200 c.c.; b. p. 40—60°) was poured down an alumina column (2 × 25 cm.). Elution with the same solvent, followed by recrystallisation, gave first 2-nitrodiphenyl, m. p. and mixed m. p. 36·5°, and then 4-nitrodiphenyl, m. p. and mixed m. p. 110—112°.

(ii) *Quantitative.* Reactions were carried out in duplicate in a thermostat maintained at 125° ± 0·1° by the method previously used by Augood, Hey, and Williams (*loc. cit.*). The reaction flasks containing the nitrobenzene (150 c.c.) were placed in the thermostat for 1 hr. before the addition of the lead tetrabenzoate. The addition of the tetrabenzoate (17·3 g.) was effected with vigorous stirring and then a further 50 c.c. of solvent were added dropwise. Stirring was continued for 1 hr. and the mixtures were removed from the thermostat after 15 hr., reactions being then complete. Duplicate reactions for comparison were carried out simultaneously with benzoyl peroxide (7·8 g.) in nitrobenzene (100 c.c.), under the same conditions of time and

temperature. The working-up of the four mixtures was the same as that described for the qualitative experiments. Final distillation gave mixtures of nitrodiphenyls as a yellow semi-solid, b. p. 104—124°/0·3 mm., from the lead tetrabenzoate reaction, and as an orange-coloured semi-solid, b. p. 99—128°/0·4 mm., from the benzoyl peroxide reactions. The orange-colour of the latter was not removed by chromatography. Higher phenylated products were distilled from the residues in each case as red resins, b. p. *ca.* 200°/0·4 mm. The products obtained from these reactions are listed in Table 1. Analyses for nitrogen in the mixtures of isomeric nitrodiphenyls were as follows: lead tetrabenzoate reactions (i) 7·25, (ii) 7·35; benzoyl peroxide reactions (i) 7·30, (ii) 7·35 (Calc. for $C_{12}H_9O_2N$: N, 7·0%).

The percentage of benzoate radicals accounted for in Table 1 amounts to 80·5 for the lead tetrabenzoate reaction and 77·9 for the benzoyl peroxide reaction.

The determination of the isomer ratios of the products formed in these reactions was carried out by ultra-violet spectrophotometry with the aid of a " Unicam S.P. 500 " quartz spectrometer, the method of calculation previously described (Cadogan, Hey, and Williams, *J.*, 1954, 794) being used. The absorption curves of the pure isomers have been recorded by Pestemer and Mayer-Pitsch (*Monatsh.*, 1937, **70**, 104) and by De Tar and Scheifele (*J. Amer. Chem. Soc.*, 1951, **73**, 1442). The extinction coefficients of the two mixtures from the lead tetrabenzoate reactions differed only slightly and the mean was used for purposes of calculation. The mixtures from the benzoyl peroxide reactions were treated separately. The compositions of the mixtures thus obtained are given in Table 2, the overall error in each determination being ±2%.

TABLE 1. *Products obtained in reactions with nitrobenzene at* 125°.

	$Pb(O{\cdot}CO{\cdot}Ph)_4$ reaction		$(Ph{\cdot}CO{\cdot}O)_2$ reaction	
Product	g. (mean)	Mole/mole (mean)	g. (mean)	Mole/mole (mean)
Free $Ph{\cdot}CO_2H$	3·00	0·985	2·89	0·74
$Ph{\cdot}CO_2H$ from ester	0·53	0·17	0·45	0·11
$Ph{\cdot}C_6H_4{\cdot}NO_2$	2·13	0·43	4·15	0·65
Higher phenylated products ...	0·10	0·01 *	0·29	0·03 *

* Calculated as $Ph{\cdot}C_6H_4{\cdot}C_6H_4{\cdot}NO_2$.

TABLE 2. *Isomer ratios in reactions with nitrobenzene at* 125°.

	Isomers (%)		
Reaction	*ortho*	*meta*	*para*
Lead tetrabenzoate reaction (mean)	55	16	29
Benzoyl peroxide reaction (1)	57·4	15·4	27·2
Benzoyl peroxide reaction (2)	55·3	16·0	28·7
Benzoyl peroxide reaction (mean)	56·3	15·7	28·0

Action of Lead Tetrabenzoate on Butane-2 : 3-diol.—Butane-2 : 3-diol (9 g.) in dry dioxan (30 c.c.) was added dropwise to a suspension of lead tetrabenzoate (20·6 g.) in dry dioxan (50 c.c.) stirred vigorously at 15°, precautions being taken to avoid loss of acetaldehyde. The yellow colour of the tetrabenzoate gradually faded and the white dibenzoate formed dissolved after 1 hour's stirring. The clear solution was left overnight, diluted to 250 c.c. with water, and filtered. The residue of lead dibenzoate and benzoic acid was washed with water and the combined filtrates were made up to 2 l. The acetaldehyde was estimated gravimetrically as the dimedone derivative, which without crystallisation had m. p. and mixed m. p. 139—140° (anhydride, m. p. 176°), and corresponded to 78% of theory. The glycol could also be oxidised in 20% aqueous solution without hydrolysis of the lead tetrabenzoate (cf. Baer, Groscheintz, and Fisher, *J. Amer. Chem. Soc.*, 1939, **61**, 2607), which is evidence of a reaction even more rapid than the hydrolysis of the oxidising agent which occurs very readily.

Action of Benzoyl Peroxide on Butane-2 : 3-diol.—When the suspension of benzoyl peroxide (25 g.) in butane-2 : 3-diol (50 g.) was heated slowly to 80° under reflux a vigorous reaction started and the temperature rose to 140°. After the reaction had subsided the mixture was heated at 95° for 1 hr. Distillation gave: (i) a fraction, b. p. 80—100°/760 mm., which contained diacetyl (semicarbazone, m. p. and mixed m. p. 272°) and benzene (*m*-dinitrobenzene, m. p. and mixed m. p. 90°), but no acetaldehyde (negative dimedone reaction); (ii) a fraction, b. p. 100°/760 mm. to 60°/20 mm., which contained acetoin (semicarbazone, m. p. 189°; osazone, m. p. and mixed m. p. 243°); and (iii) a fraction, b. p. 60—80°/20 mm., which contained diphenyl, m. p. and mixed m. p. 68°. The residue was dissolved in aqueous sodium hydroxide, washed with ether,

and acidified in stages. The first acidic precipitate gave diphenyl-4-carboxylic acid, m. p. and mixed m. p. 224—225° after crystallisation from benzene–light petroleum (b. p. 60—80°); the subsequent precipitates consisted of benzoic acid, m. p. and mixed m. p. 120°.

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Investigation on the Co-ordinative Power of Uranyl. Part II. Absorption Spectra of the Complexes with β-Diketones.*

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[Reprint Order No. 5105.]

Absorption spectra of anhydrous and aqueous organic solutions of uranyl complexes afford experimental evidence of the existence of strong bonds (essentially covalent) between the uranium central atom and the ligands, and show that the complexes are solvated and hydrated to a high degree. This supports the conclusion that in such complexes uranium(VI) exhibits a co-ordination number greater than 6.

THE study of the spectra of uranyl compounds has thrown light on their constitution and on the character of bonds, the interaction with solvents, etc. (cf. Dieke and Duncan, "Spectroscopic Properties of Uranium Compounds," McGraw Hill, New York, 1949; Kiss and Nyiri, *Z. anorg. Chem.*, 1942, **249**, 340), and we have therefore carried out spectrophotometric measurements on solutions of these compounds and various β-diketones in order to obtain information on the complexes so formed.

EXPERIMENTAL

Visible and ultra-violet absorption spectra of solutions of the complexes referred in Part I * were measured with a Beckman DU quartz spectrophotometer and silica cells 0·999 cm. long.

Methyl and ethyl alcohols and ethyl ether used as solvents were carefully purified (cf. Harrison, Lord, and Loofbourow, "Practical Spectroscopy," Prentice-Hall, New York, 1948, p. 418). Aqueous solvents were: 98% methyl and ethyl alcohols, and diethyl ether (saturated with water at 20—22°). The solutions were $16{\cdot}9 \times 10^{-2}$ mM with respect to β-diketones and half this concentration (*i.e.*, equivalent) with respect to uranyl complexes.

TABLE 1.

Compound	Solvent *	λ (mμ)	log ε	λ (mμ)	log ε	Compound	Solvent *	λ (mμ)	log ε	λ (mμ)	log ε
Picolinoylacetone	A, B	225	3·77	313	4·13	Benzoylpicolinoyl-methane	A, B, C, D, E, F	245	3·91	341	4·31
Nicotinoylacetone	A, B, C	236	3·80	307	4·14			245	3·90	341	4·31
		236	3·79	307	4·13			245	3·92	341	4·35
		236	3·80	307	4·13			245	3·92	341	4·36
5-Acetoacetyl-3-methyl*iso*-oxazole	A, B, D	249	3·71	310	4·10			237	3·91	342	4·29
		249	3·72	310	4·11			237	3·90	342	4·28
		249	3·74	310	4·13	Benzoylnicotinoyl-methane	A, B, C	246	3·90	339	4·27
5-Benzoylacetyl-3-methyl*iso*-oxazole	A, B, D, E	256	3·85	340	4·25			246	3·89	339	4·27
		256	3·85	340	4·25			246	3·91	339	4·27
		256	3·86	340	4·25						

* A = Anhydrous EtOH; B = 98% EtOH; C = anhydrous MeOH; D = aqueous Et_2O; E = anhydrous Et_2O; F = 98% MeOH.

In Table 1 are given spectral positions (in mμ) and intensities (in log ε/M) of characteristic maxima for the β-diketones. Experimental absorption curves for β-diketones and complexes are shown in the Figures and recorded in Table 2, where *D* signifies optical density. β-Diketones dissolved in different solvents give almost identical curves, so only one curve is given for each.

* Part I *J.*, 1954, 2368.

TABLE 2.

Reagents and complexes *	Solvent †	$\lambda_{max.}$	D	$\lambda_{min.}$	D	$\lambda_{max.}$	D	$\lambda_{min.}$	D	$\lambda_{max.}$	D
Benzoylacetone	A, B	248	0·96	263	0·61	309	2·34	—	—	—	—
$UO_2(benzac)_2$	A	263	1·65	280	1·54	305	1·66	355	0·61	377	0·69
,,	B	250	1·37	260	1·27	308	2·11	360	0·35	378	0·38
Benzoylacetone	D, E	248	1·00	264	0·67	309	2·42	—	—	—	—
$UO_2(benzac)_2$	E	258	1·82	290	1·48	303	1·53	355	0·61	378	0·83
,,	D	251	1·49	262	1·34	307	2·16	355	0·46	378	0·59
Benzoylacetone	C, F	248	0·98	265	0·60	309	2·20	—	—	—	—
$UO_2(benzac)_2$	C	255	1·65	280	1·62	307	1·82	355	0·59	376	0·66
,,	F	255	1·62	280	1·60	307	1·80	356	0·58	376	0·64
Dibenzoylmethane	A, B	253	1·46	275	0·80	342	>3·0	—	—	—	—
$UO_2(dimet)_2$	A	275	2·55	310	1·64	334	2·04	365	1·27	394	1·50
,,	B	257	1·98	300	1·64	340	>3·0	387	0·83	394	0·84
Dibenzoylmethane	D, E	253	1·53	275	0·80	340	>3·0	—	—	—	—
$UO_2(dimet)_2$	E	269	2·91	305	1·51	334	2·07	360	1·23	396	1·88
,,	D	261	2·40	300	1·52	334	2·66	380	1·17	396	1·30
Dibenzoylmethane	C, F	253	1·51	275	0·81	342	>3·0	—	—	—	—
$UO_2(dimet)_2$	C	269	2·45	305	1·66	336	2·16	375	1·33	395	1·45
,,	F	269	2·45	305	1·71	336	2·25	375	1·33	394	1·45
Picolinoylacetone	A, B	228	1·00	258	0·46	317	2·20	—	—	—	—
$UO_2(picac)_2$	A	246	1·69	265	1·07	316	1·48	360	0·76	376	0·80
,,	B	237	1·46	260	1·00	310	1·85	365	0·47	380	0·51
,,	C	243	1·39	265	0·91	314	1·44	360	0·56	376	0·58
Nicotinoylacetone	A, B	236	1·03	254	0·41	307	2·25	—	—	—	—
$UO_2(nicac)_2$	A	250	1·61	283	0·96	323	1·50	—	—	—	—
,,	B	240	1·55	270	1·19	307	1·67	360	0·48	378	0·57
,,	C	247	1·66	280	1·14	308	1·42	355	0·58	376	0·68
5-Acetoacetyl-3-methyl-*iso*oxazole	A, B	249	0·86	266	0·54	310	2·11	—	—	—	—
,, ,,	D, E	249	0·92	266	0·85	310	2·43	—	—	—	—
$UO_2(isoxac)_2$	A	261	1·66	290	1·15	320	1·37	350	0·72	378	0·89
,,	E	266	1·71	290	1·19	306	1·31	314	1·29	320	1·31
								350	0·62	378	0·96
,,	D	266	1·66	285	1·32	306	1·55	350	0·59	378	0·89
Nicotinoylbenzoylmethane	A, B, C	246	1·34	280	0·74	339	3·10	—	—	—	—
$UO_2(nicmetH)_2(NO_3)_2$	A, B	253	1·60	220	1·38	335	2·78	385	0·75	399	0·84
,,	C	260	1·87	298	1·58	336	2·60	383	1·04	396	1·13
5-Benzoylacetyl-3-methyl-*iso*oxazole	A, B	256	1·19	280	0·75	340	2·98	—	—	—	—
$UO_2(isoxmet)$	A, B	280	2·27	312	1·32	333	1·64	360	1·10	395	1·70
5-Benzoylacetyl-3-methyl-*iso*oxazole	D, E	256	1·23	280	0·26	340	2·98	—	—	—	—
$UO_2(isoxmet)_2$	E	280	2·61	310	1·35	333	1·79	360	1·04	397	1·95
,,	D	277	2·28	308	1·30	333	1·86	363	1·15	397	1·65

* For abbreviations, see Part I (pp 2369—2370). † See Table 1.

RESULTS AND DISCUSSION

(1) The spectra obtained for the β-diketones have essentially the same general shape and show two bands, one in the 225—256-mμ and the other in the 307—349-mμ region. Values for benzoylacetone and dibenzoylmethane agree with those recorded by Morton *et al.* (*J.*, 1934, 883), according to whom the absorbing entities are complex chromophores. The 225—256-mμ maximum was ascribed to the phenyl group influenced by the carbonyl group, and that near 307—349 mμ to the carbonyl group. In terms of modern views, the absorption maximum at 307—349 mμ should be referred to the enol form of the β-diketones, stabilized through a chelation involving a hydrogen bond. The resulting enol ring is then stabilized through both hydrogen-bond formation and enol resonance (cf. Ferguson, "Electron Structure of Organic Molecules," Prentice-Hall, New York, 1952, pp. 216, 218).

(2) The nature of the solvent (methanol, ethanol, and ethyl ether, anhydrous or aqueous) scarcely affects the spectra of diketones, particularly those of benzoylacetone and dibenzoylmethane. This last fact is probably associated with the absence of polar atoms in the groups attached to the carbonyl carbon atom of both β-diketones, which produces weaker interaction with the molecules of the polar solvents.

(3) The absorption curves obtained for the complexes, except those of benzoylpicolinoylmethane, show three bands, at 240—280, 303—340, and 376—403 mμ, respectively. The first two correspond essentially to those of the complexing agents, but the first is shifted

FIG. 1. FIG. 2. FIG. 3.

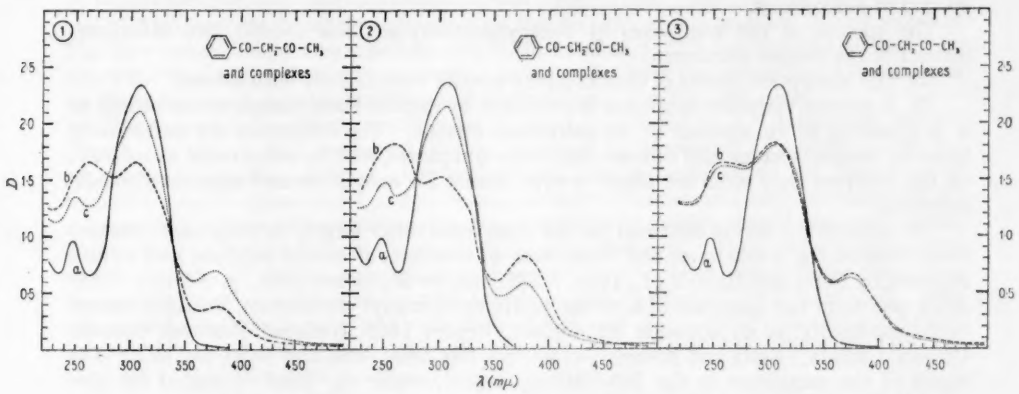

FIG. 1. *a*, Benzoylacetone in anhydrous and 98% EtOH; *b*, $UO_2(benzac)_2$ in anhydrous EtOH; *c*, $UO_2(benzac)_2$ in 98% EtOH.

FIG. 2. *a*, Benzoylacetone in anhydrous and aqueous Et_2O; *b*, $UO_2(benzac)_2$ in anhydrous Et_2O; *c*, $UO_2(benzac)_2$ in aqueous Et_2O.

FIG. 3. *a*, Benzoylacetone in anhydrous and 98% MeOH; *b*, $UO_2(benzac)_2$ in anhydrous MeOH; *c*, $UO_2(benzac)_2$ in 98% MeOH.

FIG. 4. FIG. 5. FIG. 6.

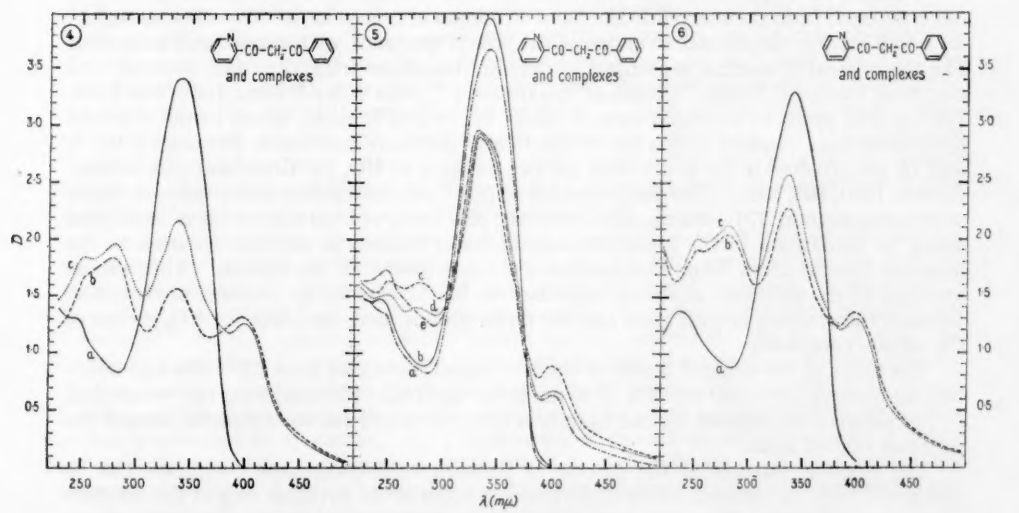

FIG. 4. *a*, Benzoylpicolinoylmethane in anhydrous and 98% EtOH; *b*, $UO_2(picmet)_2$ in anhydrous EtOH; *c*, $UO_2(picmet)_2$ in 98% EtOH.

FIG. 5. *a*, Benzoylpicolinoylmethane in anhydrous Et_2O; *b*, Benzoylpicolinoylmethane in aqueous Et_2O; *c*, $UO_2(picmetH)_2(NO_3)_2$ in anhydrous EtOH; *d*, $UO_2(picmetH)_2(NO_3)_2$ in 98% EtOH; *e*, $UO_2(picmetH)_2(NO_3)_2$ in aqueous Et_2O.

FIG. 6. *a*, Benzoylpicolinoylmethane in anhydrous and 98% MeOH; *b*, $UO_2(picmetH)_2(NO_3)_2$ in anhydrous MeOH; *c*, $UO_2(picmetH)_2(NO_3)_2$ in 98% MeOH.

towards longer wave-lengths with a hyperchromic effect; the second is shifted generally towards shorter wave-lengths with a hypochromic effect. The third band is lacking in the spectra of β-diketones.

The spectra of the complexes of benzoylpicolinoylmethane exhibit two inflections instead of the former maximum.

(4) The absorption curves of each complex usually vary slightly with solvent.

(5) A greater variation in spectra is exhibited by each of these complexes according as it is dissolved in an aqueous or an anhydrous solvent. The differences are particularly large for benzoylacetone and dibenzoylmethane complexes, and for ethyl ether as solvent; on the contrary they often are slight or even absent for anhydrous and aqueous-alcoholic solutions.

The absorption curves obtained for the complexes differ largely in shape and features from those of the β-diketones and from those of solutions of uranyl sulphate and nitrate reported by Betts and Michels (*J.*, 1949, S 282) and by Mathieson (*ibid.*, p. S 298). They differ also from the spectrum of aqueous solutions of uranyl perchlorate, in which uranyl exists essentially as an aquo-ion (cf. Sutton, Report 1612, National Research Council, Ottawa, Canada; Betts and Michels, *loc. cit.*, pp. 288, 289; Kiss and Nyiri, *loc. cit.*). The bands of the complexes in the 303—340-mμ region, where the band of uranyl ion also occurs, show a negative effect, being less intense than those of the β-diketones at 307—349 mμ.

In the spectra of the complexes, instead of the assembly of eleven bands of uranyl with a maximum at *ca.* 416 mμ, there appears a band with the maximum shifted toward shorter wave-lengths, at 376—403 mμ. According to Ferguson (*op. cit.*, p. 46), this decrease in the wave-length of the maximum reflects chelation between the central atom and the ligands. It can be assumed that this new band is produced from some new electron transition which accompanies the interaction of the chelate groups with the uranium central atom. The stability of the complexes should be proportional to this hypsochromic effect.

It should be emphasized that this band shows a continuous shape without structure, quite different from the sharp line-like band envelopes of uranyl in the 360—490-mμ region. As is well known, the distinct structure of the uranyl spectrum, with sharp bands somewhat like the rare-earth spectra, is ascribed to definite transitions from vibration, rotation, and electronic levels (cf. Brode, " Chemical Spectroscopy," John Wiley & Sons, Inc., New York, 1947, p. 267) owing to incompleteness of the 5*f*, 6*d*, 7*s*, and 7*p* shells, which permit electron-level transitions. Indeed, only a part of the 16 orbitals above mentioned, presumably the 7*s* and 7*p*, are involved in the bonds with the two oxygens of UO_2 (cf. Glueckauf and McKay, *Nature*, 1950, **165**, 594). The disappearance of this distinct structure in the uniform bands of the complexes at 376—403 mμ shows that the possibility of level transitions is diminished owing to diminution in the incompleteness of levels because of electron-donation to the uranium central atom from electron-donor oxygen atoms of the ligands. This affords evidence of the existence of strong co-ordinative bonds, essentially covalent in character, between the uranium central atom and the donor groups, here including the NO_3 groups of the nitrate complexes.

The shifts of the original bands of the free ligand molecules from 225—256 and 307—349 mμ towards 240—280 and 303—340 mμ in the spectra of the complexes can be ascribed to the polarization suffered by the ligands in consequence of the co-ordination around the uranium central atom.

The singular features of the spectra of benzoylpicolinoylmethane complexes can be correlated with the presence of the *ortho*-nitrogen atom in the pyridinic ring of the diketone molecule. Since the maximum near 280 mμ is lacking in the spectra of the ligand, we can assume that such a feature is due to interactions between the nitrogen atom and the uranium central atom.

The change in the absorption curve for each complex, especially for the complexes of benzoylacetone and dibenzoylmethane, from solvent to solvent, and the larger change when an anhydrous solvent is substituted for the aqueous one, reflects the strong interaction between the molecules of the complex and those of the organic solvent or water, which results in solvation.

In the case of the curves of aqueous ethanol and ethyl ether solutions of the complexes of benzoylacetone and dibenzoylmethane, the hypochromic effect on the band near 263 and 270 mμ and the hyperchromic effect on the maxima at 305 and 336 mμ are notable. The very remarkable decrease in intensity of the maxima at 378 and 390 mμ, respectively, above ascribed to the chelated uranium(VI), as compared with the intensities of the maxima for the solutions in the same anhydrous solvents, should also be emphasized.

This hypochromic effect, which could be even considered as a " dampening effect " (Brode, *op. cit.*, p. 231) analogous to that observed by Mathieson (*J.*, 1949, S 298) for organic and aqueous solutions of uranyl nitrate, can be ascribed to the formation of hydrates, *i.e.*, to replacement of the bonds between uranium and organic molecules by stronger bonds between uranium and water, a substitution which should cause a lowering of the vibrational properties of the electronic system of uranyl. Thus, these experimental results suggest that, in aqueous-organic solutions of the complexes, water molecules replace the organic " solvation " molecules, with formation of a " primary " hydration shell. This agrees with Glueckauf's views and with those of Katzin *et al.* (*J. Phys. Colloid Chem.*, 1951, **51**, 346; *Trans. Faraday Soc.*, 1951, **47**, 438; *J. Amer. Chem. Soc.*, 1952, **74**, 1191) on solutions of uranyl nitrate in aqueous organic solvents.

As mentioned above, the change in spectra from anhydrous to aqueous solutions is very strong for the complexes of benzoylacetone and dibenzoylmethane. Since these ligands when bound in the complexes have no polar atoms capable of strong interactions with the solvent molecules, the view is supported that the observed interactions occur between water or organic molecules and the uranium central atom, and therefore that they are co-ordinative in nature. Thus the co-ordinative unsaturation of uranium(VI) bound in these complexes is further supported.

This effect is much less evident, or even absent, in the spectra of alcoholic solutions. This fact is analogous to anomalous behaviour of uranyl nitrate–water–alcohol systems, referred by Katzin and Sullivan (*J. Phys. Coll. Chem.*, 1951, **55**, 346), Mathieson and McKay (*Trans. Faraday Soc.*, 1951, **47**, 428), and Glueckauf, McKay, and Mathieson (*ibid.*, p. 437). According to the assumption of these authors in the case of aqueous-alcoholic solutions of uranyl nitrate, it may be assumed that, for such solutions of uranyl complexes too, a competition exits between the molecules of alcohol and the molecules of water co-ordinated around the uranium central atom, *i.e.*, that alcohol molecules, by virtue of their hydroxyl groups, can replace some water of hydration. In this way, the " primary " solvation shell will not differ greatly from anhydrous to aqueous alcohol solutions. This assumption explains the similarity between several of the spectra of such complexes in anhydrous and in aqueous-alcohol solutions.

The fact that absence of change in spectrum of complexes has been found chiefly for anhydrous and aqueous methyl alcohol solutions, can be fully explained on the basis of steric considerations. Indeed, the small size of the methanol molecules, in contrast to that of ethanol, allows them to penetrate more easily as far as the uranium central atom " screened " by the voluminous donor groups packed around it. In such a way the methanol molecules will be able to compete with the hydrating molecules and displace them.

Conclusions.—From these spectrophotometric investigations we conclude that: (1) The co-ordination bonds between the uranium central atom and the ligands are strong, probably covalent in character. (2) The complexes, in various anhydrous and aqueous solvents, have a high tendency to form solvates and hydrates. (3) The attractions between uranium and water molecules and between uranium and organic molecules are rather strong and should be considered as co-ordinative forces. (4) Uranium(VI) in these complexes has a tendency to manifest a co-ordination number greater than 6.

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A Comparison of the Mechanisms of the Solvolytic Hydrolysis Reactions of Acetic Anhydride and Benzoyl Chloride.

By V. Gold, J. Hilton, and E. G. Jefferson.

[Reprint Order No. 5182.]

The hydrolysis of benzoyl chloride and acetic anhydride in aqueous acetone has been studied kinetically. By examining the influence of different amounts of an added aromatic amine (which can compete with the solvent for the acylating agent) on the rate and on the final product composition, it has been possible to determine the relative contributions of unimolecular and bimolecular mechanisms to the acylation of the amine and to the acylation of water. Acetic anhydride in acetone–water (50 : 50 w/w), and benzoyl chloride in acetone–water (80 : 20 w/w) react by bimolecular mechanisms, but in the hydrolysis of benzoyl chloride in acetone–water (50 : 50 w/w) approximately half of the total reaction proceeds by a rate-determining process in the benzoyl chloride molecule, which does not involve participation of the molecule undergoing acylation. The analysis shows that it is preferable to regard a border-line (*i.e.*, between S_N1 and S_N2) solvolysis to be the sum of two simultaneously occurring processes rather than as a single reaction involving an intermediate degree of solvent participation.

The use of the relation between log k and $(\varepsilon - 1)/(2\varepsilon + 1)$ (ε = dielectric constant) as a criterion of reaction mechanism is discussed, and it is concluded that in the present state of knowledge the existence of a non-linear relation between these two quantities is insufficient evidence for a change of mechanism. For the hydrolysis of benzoyl chloride the application of this method leads to the same conclusion as the kinetic analysis of the competition experiments.

The unambiguous assignment of a detailed mechanism to a reaction between two species in a condensed phase is more difficult when the reaction partners are a solvent and a solute species than when both are solutes in low concentration. In the former case, the variation of the stoicheiometric concentration of one of the species by an order of magnitude or so is usually attended by a large change in the properties of the medium * and, therefore, the molecularity of the reaction with respect to the solvent cannot be deduced from the relation between concentration and reaction velocity. In addition to a consequent "medium effect" on the rate there is also the problem as to what kind of a concentration scale is a correct measure of the collision frequency or *a priori* probability of the activation process. This problem does not arise in reactions between solutes, since at sufficiently low concentrations the molarity, molality, mole fraction, volume fraction, partial vapour pressure, etc., are nearly proportional to each other and a satisfactory analysis of the reaction in terms of reaction order is possible whatever concentration scale is used.

For these reasons less direct methods for determining the molecularity of a reaction with respect to a solvent are usually employed (see Hughes, *Trans. Faraday Soc.*, 1941, **37**, 611). Not all these methods are useful in every instance. The applications of some of them to the hydrolysis of acetic anhydride (Gold, *ibid.*, 1948, **44**, 506) and to that of benzoyl chloride (Hudson and Wardill, *J.*, 1950, 1729; Archer and Hudson, *ibid.*, p. 3259; Brown and Hudson, *J.*, 1953, 883; Archer, Hudson, and Wardill, *ibid.*, p. 888) have recently been discussed. However, some of these criteria of mechanism are rather indirect and, moreover, are diagnostic only in a qualitative fashion; *i.e.*, they do not allow the quantitative analysis of a border-line case where processes of different mechanism may proceed

* Although it may be unsound to draw a sharp division between "solutes" and "solvents," the foregoing statement appears to provide a useful distinction for the purpose of chemical kinetics in solution. The solution property whose variation is significant in this connection is the rate in that solution of a similar but non-solvolytic reaction.

simultaneously, as has been suggested for the hydrolysis of benzoyl chloride in certain acetone–water mixtures (Hudson *et al.*, *locc. cit.*).

A method, applicable to acylation reactions, which is independent of these indirect criteria of mechanism and allows at the same time an estimate of the relative importance of two simultaneously occurring different mechanisms, has accordingly been developed. Such a direct approach has also seemed desirable in view of certain doubts which have been raised regarding the physical meaning of the molecularity of a reaction with respect to the solvent (Winstein, Grunwald, and Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700).

With regard to terminology: we recognise that solvent molecules play a part in all reactions in solution, *i.e.*, even in so-called unimolecular solvolyses (*e.g.*, S_N1). Nevertheless, since the slow first step in these reactions is not peculiar to solvolysis but is common to all reactions proceeding by this mechanism, irrespective of whether the subsequent reaction of the ion is with a solvent or a solute, these reactions have continued to be called unimolecular.

The experimental procedure followed consisted in examining the influence of varying concentrations of a solute aromatic amine, which competes with the water in the solvent for the acylating agent, on (i) the total velocity of the disappearance of the acylating agent, and (ii) the relative amounts of the reaction products (anilide and acid).

The study of the intervention of azide ions in the unimolecular solvolysis of alkyl halides (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979; Hawdon, Hughes, and Ingold, *J.*, 1952, 2499) illustrates another application of the same basic approach.

For the sake of definiteness, let us represent the relevant mechanisms for benzoyl chloride by the following chemical equations, although it will be seen later that a slightly different interpretation of the data would also be acceptable.

Bimolecular (S_N2): $BzCl + H_2O \xrightarrow{k_2} BzOH + HCl$

$BzCl + R{\cdot}NH_2 \xrightarrow{k_2'} Bz{\cdot}NHR + HCl$

Unimolecular (S_N1): $BzCl \xrightarrow{k_1} Bz^+ + Cl^-$

$Bz^+ + H_2O \xrightarrow{\kappa_1} BzOH + H^+$

$Bz^+ + R{\cdot}NH_2 \xrightarrow{\kappa_1'} Bz{\cdot}NHR + H^+$

The symbol above a reaction arrow represents the rate constant of the reaction concerned, which is supposed to be of the molecularity indicated by the stoicheiometry. The acylation reactions of acetic anhydride may be written in an analogous manner. The proved absence of common-ion effects in the hydrolysis of benzoyl chloride (Table 3; cf. Archer, Hudson, and Wardill, *loc. cit.*) allows us to disregard the association reaction between Bz^+ and Cl^- ions.

The kinetic features of the simultaneous occurrence of the above two mechanisms are then represented by the following set of equations. Let x and y be the concentration changes of the acylating agent A, due to hydrolysis and anilide formation respectively. The concentrations of acylating agent and amine are denoted by a and b respectively; w stands for the concentration of water in the appropriate (unspecified) units, as discussed above. The subscripts 0 and ∞ used in connection with concentration symbols refer to times from the mixing of the reagents:

$$dx/dt = k_1 a\kappa_1 w/(\kappa_1 w + \kappa_1' b) + k_2 a w \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$dy/dt = k_1 a\, \kappa_1' b/(\kappa_1 w + \kappa_1' b) + k_2' a b \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where the first term on the right-hand side of each expression accounts for the unimolecular portion of the reaction and the second term for the bimolecular one. If b and w can be assumed to remain constant during the reactions the total reaction velocities in the absence and in the presence of amine will follow the first-order law. The respective first-order rate

constants k_H and k_T will be related to the rate constants of the fundamental steps of the above reaction scheme:

$$k_H = k_1 + k_2w \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$k_T = k_1 + k_2w + k_2'b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Also, from (1) and (2):

$$\frac{dx}{dy} = \frac{k_2w + k_1\kappa_1w/(\kappa_1w + \kappa_1'b)}{k_2'b + k_1\kappa_1'b/(\kappa_1w + \kappa_1'b)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and, if w and b can again be assumed to stay sensibly constant during the course of the reaction or, at least, to be adequately represented by a mean value, integration is possible and

$$\frac{dx}{dy} = \frac{x_\infty}{y_\infty} = \frac{\%\ \text{Hydrolysis}}{\%\ \text{Anilide formation}} \equiv \rho \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

[This integrated expression is *not* equivalent to the expression previously given (Emery and Gold, *J.*, 1950, 1449), which was derived on the assumption that only one mechanism operates, although the nature of the mechanism was immaterial.] The product ratio ρ can be determined by acidimetry of the solution after completion of the reaction. The extent of conversion of the amines into their conjugate acids was negligible.

It will at first be assumed that the addition of aromatic amine does not change the rate of hydrolysis for a given acetone–water mixture, *i.e.*, that the medium properties and the kinetically effective water concentration are unaffected. Then, for a given solvent mixture, $k_2'b = k_T - k_H$. The large value of this difference between k_T and k_H for moderate values of b demonstrates that a significant amount of bimolecular acylation occurs for all the conditions studied by us (Table 1). Equations (3)—(6) can also be combined to give

$$k_1 \cdot \frac{\kappa_1'b}{\kappa_1w + \kappa_1'b} = \frac{k_T}{\rho + 1} - (k_T - k_H) \equiv \chi \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

which allows the unimolecular contribution to the amine acylation reaction to be deduced. The evaluation of χ from the experimental data is given in Table 2.

TABLE 1. *Dependence of overall rate of disappearance of acylating agent on concentration of added amine.*

Acetic anhydride: B = *o*-Chloroaniline. Temp.: 30·06°. Solvent: acetone–water (50 : 50 w/w). $[Ac_2O]_0$ ~0·04M.

$[B]_{mean}$ *	0	0·086	0·118	0·466
10^4k_T (sec.$^{-1}$)	1·39	3·58	4·65	10·4

Benzoyl chloride: B = *o*-Nitroaniline. Temp.: 0°. $[BzCl]_0$ ~0·05M.

Wt. (%) of acetone in solvent					
80	$[B]_{mean}$ *	0	0·091	0·187	0·285
	10^5k_T (sec.$^{-1}$)	3·9	6·5	8·0	10·0
50	$[B]_{mean}$ *	0	0·092	0·188	0·286
	10^5k_T	27·7	32·1	36·3	39·6

* In some of the experiments the concentration of amine was not in large excess over the concentration of acylating agent. The mean concentration of amine in these experiments was calculated from the independent determination of ρ. The rate of change of the amine concentration was sufficiently small not to impair the evaluation of the first-order rate coefficient after exactly one half-life.

For acetic anhydride in acetone–water (50 : 50 w/w) and benzoyl chloride in acetone–water (80 : 20 w/w), χ is found to be zero within the experimental error. On the other hand, this analysis leads to an appreciable value for χ (amounting to up to a quarter of the total rate) in the case of benzoyl chloride in acetone–water (50 : 50 w/w), and from the dependence of χ on the concentration of added base, *viz.*,

$$1/\chi = (1 + \kappa_1w/\kappa_1'b)/k_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

it is possible to derive graphically that $k_1 = (14{\cdot}5 \pm \frac{4}{9}) \times 10^{-5}$ sec.$^{-1}$, *i.e.*, that in the hydrolysis of benzoyl chloride in acetone–water (50 : 50 w/w) the unimolecular and the

TABLE 2. *Values of ρ and the evaluation of χ.*

Acetic anhydride in acetone–water (50 : 50 w/w) at 30·06°.

[*o*-Chloroaniline]$_{mean}$, M	10^4k_T (sec.$^{-1}$)	ρ *	$10^4k_T/(\rho + 1)$	$10^4(k_T - k_H)$	$10^4\chi$
0·086	3·58	$0·62_5$	2·20	2·19	+0·01
0·118	4·65	$0·44_5$	3·22	3·26	−0·04
0·466	10·4	$0·16_5$	8·9	9·0	−0·1

* Obtained by interpolation from a more extensive set of measurements at different concentrations.

Benzoyl chloride in acetone–water (80 : 20 w/w) at 0°.

[*o*-Nitroaniline]$_{mean}$, M	10^5k_T (sec.$^{-1}$)	ρ	$10^5k_T/(\rho + 1)$	$10^5(k_T - k_H)$	$10^5\chi$
0·091	6·5	1·88	2·3	2·6	−0·3
0·187	8·0	1·04	3·9	4·1	−0·2
0·285	10·0	$0·72_5$	5·8	6·1	−0·3

Benzoyl chloride in acetone–water (50 : 50 w/w) at 0°.

[*o*-Nitroaniline]$_{mean}$, M	10^5k_T (sec.$^{-1}$)	ρ	$10^5k_T/(\rho + 1)$	$10^5(k_T - k_H)$	$10^5\chi$
0·092	32·1	2·20	9·7	4·4	5·3
0·188	36·3	1·25	16·1	8·6	7·5
0·286	39·6	0·86	21·3	11·9	9·4

TABLE 3. *Salt effects in hydrolysis of* BzCl *in acetone–water* (50 : 50 *w/w*) *at* 0°.

Added salt :	0·1M-NaCl	0·2M-NaCl	0·3M-NaCl	0·1M-Li_2SO_4
$10^5(k_H - k°_H)$ (sec.$^{-1}$).....	1·8	2·4	2·6	2·5

TABLE 4. *First-order rate constants for the hydrolysis of benzoyl chloride in acetone–water mixtures at* 0°.

Wt. (%) of acetone in solvent	85	80	75	70	65	60	55	50	45
10^5k_H(sec.$^{-1}$)	2·6	3·9	5·4	7·4	9·5	13·2	19·4	27·7	42·6

TABLE 5. *Medium effects in the hydrolysis of benzoyl chloride and acetic anhydride in* 50% *acetone–water at* 0°.*

	Added substance	Percentage reduction † of k_H, $100(k_H - k°_H)/k°_H$
Benzoyl chloride	0·08M-Nitrobenzene	7
Acetic anhydride	0·08M-Nitrobenzene	4
,, ...	0·30M-Nitroaniline	6

* Experiments carried out by Mr. D. Bethell.

† Each of these values is the mean of several pairs of experiments agreeing to within approx. 1·5%.

bimolecular mechanism are of roughly equal importance. In principle, it should also be possible to obtain in this way the values of k_2w/k_2' and κ_1w/κ_1', *i.e.*, the relative reactivities of water and aromatic amine for benzoyl chloride and benzoylium ions, but the accuracy of the derived quantities is inadequate for this purpose. It seems, however, that the two ratios have rather similar values.

Medium Effects.—To allow for the possibility that the addition of a certain concentration of amine might exert a medium effect, equations (4), (6), and (7) may, as a second approximation, be modified to give

$$k_T = k_1(1 - \lambda) + k_2(1 - \mu)w + k_2'(1 - \nu)b \quad . \quad . \quad . \quad . \quad . \quad (4')$$

$$\rho = \frac{k_2(1 - \mu)w + k_1(1 - \lambda) \cdot \kappa_1w/(\kappa_1w + \kappa_1'b)}{k_2'(1 - \nu)b + k_1(1 - \lambda) \cdot \kappa_1'b/(\kappa_1w + \kappa_1'b)} \quad . \quad . \quad . \quad . \quad (6')$$

$$\chi = k_1(1 - \lambda) \cdot \kappa_1'b/(\kappa_1'w + \kappa_1'b) + k_1\lambda + k_2\mu \quad . \quad . \quad . \quad . \quad (7')$$

where χ, μ, and ν express the (retarding) medium effects.

It follows from equation (7′) that an appreciable value of χ could arise even when there is no unimolecular contribution to the rate at all (*i.e.*, $k_1 = 0$) in the event of μ being positive and large. Although it would be very difficult to allow rigorously for the effect of λ and μ on the value of the unimolecular contribution to the amine acylation calculated by the previous analysis, yet the following experiments render it exceedingly unlikely that this supposedly unimolecular rate is entirely, or for the most part, attributable to the medium effect of *o*-nitroaniline, *i.e.*, to the term $k_2\mu$ in equation (7′).

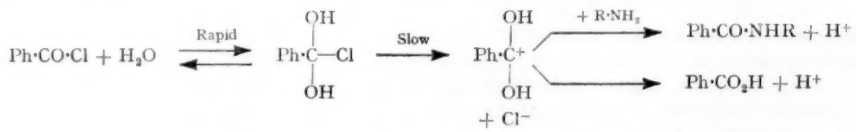
Table 5 shows the effect of added substances on the rates of hydrolysis of acetic

anhydride and benzoyl chloride. It is seen from this that the addition of 0·3M-*o*-nitroaniline (which does not undergo acylation under these conditions) reduced the rate of hydrolysis of acetic anhydride only slightly more than the addition of 0·08M-nitrobenzene. The effect of 0·08M-nitrobenzene on the rate of hydrolysis of benzoyl chloride can be measured and, in view of the similarity of the two hydrolyses, it seems justifiable to conclude that 0·286M-*o*-nitroaniline would depress the bimolecular hydrolysis of benzoyl chloride by not more than 12—14% at the most. On the other hand, it would be necessary to assume that this value is about 34% if one were to account for the value of χ found in the competition experiment with that concentration of *o*-nitroaniline on the basis of a medium effect alone.

Further support for the view that χ is not the consequence of a medium effect comes from the close agreement between $(k_T - k_H)$ and $k_T/(\rho + 1)$ for acetic anhydride in 50% acetone–water and for benzoyl chloride in 80% acetone–water, *i.e.*, under conditions where an ionisation mechanism is expected to be less likely.

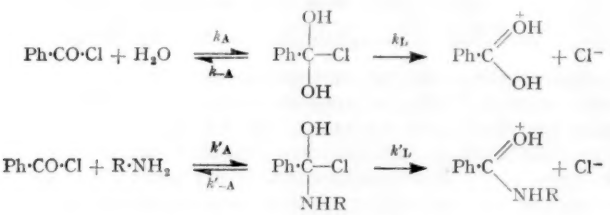
We estimate from the data of Table 5 that the value of k_1 for the hydrolysis of benzoyl chloride in 50% acetone–water, calculated above without consideration of the medium effect, is only slightly too large, and that the corrected figure would be $(11 \pm \frac{4}{2}) \times 10^{-5}$ sec.$^{-1}$. It is possible to consider more quantitative methods of analysing the data, but this seems hardly justified by their experimental accuracy.

Chemical Interpretations of Kinetic Results.—The immediate inference from the kinetic analysis for benzoyl chloride in 50% acetone–water is that some of the reaction proceeds by a mechanism in which the rate-determining step is the same and independent of amine concentration whether the outcome of the reaction is the acylation of amine or of water, and that some of it goes by a mechanism in which the rate-determining steps are different for the two reactions, that of amine benzoylation being kinetically of the first order with respect to the amine. It is impossible to decide from the results whether benzoyl chloride is first converted by one or more rapid equilibria into some intermediate which then undergoes the rate-determining process common to amine acylation and hydrolysis. However, the most reasonable rate-determining step is the heterolysis of the C–Cl bond and the assumption of a rapid and reversible intermediate hydration of benzoyl chloride preceding this step, *i.e.*,



does not appear attractive when it is remembered that the conjugate acid of benzoic acid (formed, for instance, in solutions of benzoic acid in sulphuric acid) is not a particularly good benzoylating agent.

On the other hand, it is not incompatible with the results that the bimolecular mechanism is composite, involving, as in the case of ester hydrolysis (Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626), an addition reaction as the first step, *i.e.*,

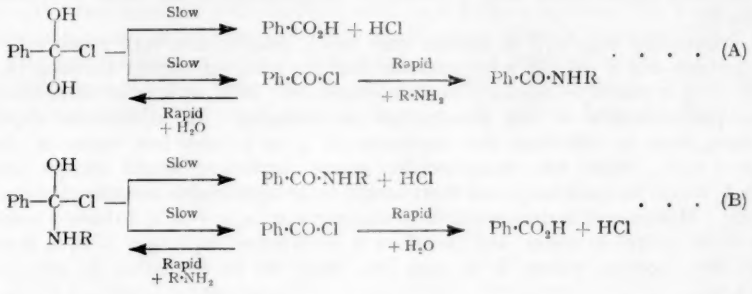


in which case the rate constants of the two bimolecular reactions are given by

$$k_2 = k_A k_L/(k_{-A} + k_L);\ k_2' = k'_A k'_L/(k'_{-A} + k'_L)$$

but, as far as our method of kinetic analysis goes, this mechanism is indistinguishable from a direct substitution mechanism.

We have also considered the mechanisms



in which it is supposed that the benzoyl chloride is virtually completely converted into adducts which then undergo unimolecular reversion to benzoyl chloride for one of the reactions. Neither of these schemes is satisfactory for the reactions of benzoyl chloride in 50% acetone–water. For instance, scheme (A) predicts $k_T/(\rho + 1)$ and $(k_T - k_H)$ to be equal, whereas scheme (B) would require $k_T/(\rho + 1)$ to be independent of the concentration of amine. Scheme (A) and more complicated schemes based on the hypothesis of rapid hydration are also rendered improbable by our observation that the instantaneous heat of mixing of benzoyl chloride and acetone–water is negligible compared with the heat of hydrolysis, the rate of evolution of which agrees with the experimental rate of hydrolysis.

Winstein, Grunwald, and Jones (*loc. cit.*) have recently suggested that it is not correct to assume two kinds of processes (*i.e.*, unimolecular and bimolecular heterolyses) to occur simultaneously in the solvolysis of " border-line " cases (*i.e.*, between S_N1 and S_N2) in any one solvent, but that it is more profitable to describe the reaction in terms of one single process, intermediate in character between the extreme mechanistic categories. A similar point has also been made by Bird, Hughes, and Ingold (*J.*, 1954, 634). It is now suggested that this approach makes too great a distinction between solvolytic and non-solvolytic reactions, and that the inadequacy of the underlying physical picture can be demonstrated by the following considerations. Let us try to apply their ideas to the situation found in the simultaneous hydrolysis and amine acylation reaction of benzoyl chloride in 50% acetone–water. Suppose the rate of hydrolysis to be given by $dx/dt = k_2^* aw^*$, where w^* is now a function of the water concentration appropriate to this intermediate type of solvent participation in the reaction. In order to explain the experimental difference between $(k_T - k_H)$ and $k_T/(\rho + 1)$ it is still necessary to assume that the rate of amine acylation be given by $dy/dt = k_2^{*\prime} ab^*$, where b^* is a function of b which increases less rapidly than the first power of b, *i.e.*, the acylation is kinetically between zero and first order. Such a reaction order cannot be attributed to an incomplete participation of an amine molecule in the transition state of the reaction: if it takes part at all, however weakly, the reaction is of the first order with respect to the amine, although other characteristics of the reaction (such as substituent effects) may indicate that the C–Cl bond rupture rather than the C–N bond formation is the more important aspect of the reaction. We are therefore bound to conclude that the intermediate reaction order indicates that amine molecules are involved in some, though not all, of the transition states of this reaction. This is equivalent to the statement that unimolecular and bimolecular acylations proceed simultaneously, *i.e.*, that

$$k_2^{*\prime} ab = k_2' b + k_1 \kappa_1' b/(\kappa_1 w + \kappa_1' b)$$

as previously derived. Now it is still conceivable that—notwithstanding the experimental evidence that some of the anilide formation proceeds *via* the intermediate formation of Bz^+ ions—none of the acylation of the solvent follows this route. This would involve the

assumption that the Bz^+ ions are infintiely more reactive towards amine than they are towards water, *i.e.*, that $\kappa_1'b \gg \kappa_1 w$ or $\kappa_1 w/\kappa_1'b \ll 1$, but this can be disproved from the experimental data by application of equation (8). If no part of the hydrolysis proceeded *via* the common unimolecular step, χ should be independent of the value of b, which it is not (Table 1).

The observation that $\kappa_1'b$ is neither very much smaller nor very much larger than $\kappa_1 w$ for acetone–water (50 : 50 w/w) confirms that the good agreement between $(k_T - k_H)$ and $k_T/(\rho + 1)$ in the experiments in acetone–water (80 : 20 w/w) is to be attributed to the complete predominance of the bimolecular mechanisms. An alternative explanation would have been to attribute the smallness of χ to a very low value of the ratio $\kappa_1'b/(\kappa_1 w + \kappa_1'b)$, when the unimolecular amine acylation would escape detection, although k_1 would be quite large and there would be an appreciable amount of unimolecular hydrolysis. However, it is unreasonable to suppose $\kappa_1 w/(\kappa_1 w + \kappa_1'b)$ to have a lower value in the solvent poorer in water, and therefore if, as is found, $\kappa_1'b/(\kappa_1 w + \kappa_1'b)$ is not very small in 50% acetone–water, it is even less likely to be negligible in acetone–water (80 : 20 w/w).

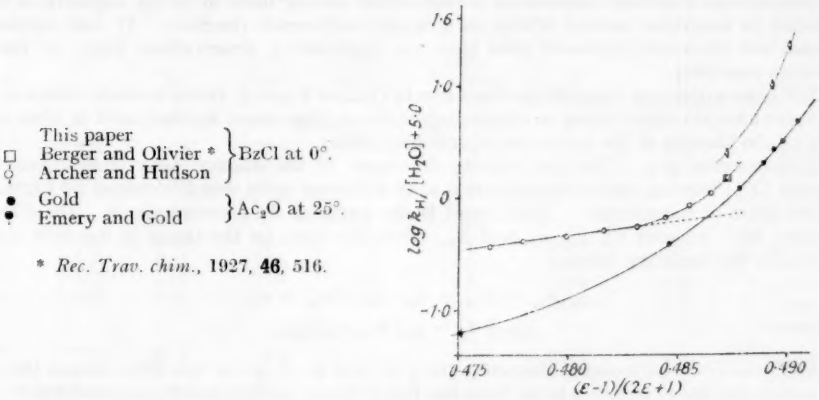
Similar considerations lead us to accept a bimolecular mechanism for the hydrolysis of acetic anhydride in 50% acetone–water.

Our demonstration of the operation of two physically distinct mechanisms in the hydrolysis of benzoyl chloride also argues against Swain and Langsdorf's point of view (*J. Amer. Chem. Soc.*, 1951, **73**, 2813) according to which " there are no clear dividing lines to distinguish between " mechanisms " such as S_N1, S_N2, $B'2$, etc." Our work links up in this respect with a recent paper by Swain, Scott, and Lohmann (*ibid.*, 1953, **75**, 136) who, by use of a kinetic technique similar to ours, employing both ionic and non-ionic competing solutes, have shown that the rate of disappearance of triphenylmethyl halides is independent of the presence of added substances although the composition of the products is thereby appreciably altered. Swain, Scott, and Lohmann draw the plausible conclusion that their results can be interpreted only by postulating an unstable intermediate which they suggest is the solvated triphenylcarbonium ion, in agreement with generally accepted views. The authors should also have pointed out that their work elegantly demonstrates an example of what is commonly known as the S_N1 mechanism and, since they implicitly accept the occurrence of a different (S_N2) mechanism in other cases (Swain and Scott, *ibid.*, p. 141), that it invalidates the earlier conclusions of Swain and Langsdorf. These, like the statement by Winstein, Grunwald, and Jones (*loc. cit.*), appear to have been founded on incorrect indirect criteria of mechanism.

The Dependence of Reaction Velocity on Dielectric Constant as a Mechanistic Criterion.—It has been suggested by Archer and Hudson (*loc. cit.*) that curvature of the relation between log k and $(\varepsilon - 1)/(2\varepsilon + 1)$ (where k is obtained by dividing the experimental rate constant by the molarity of water in the solvent) indicates a change of mechanism in a solvolytic reaction in a mixed solvent (cf. Cowan, McCabe, and Warner, *J. Amer. Chem. Soc.*, 1950, **72**, 1194). A linear relation of this form follows from Kirkwood's treatment of dipole solvation (*J. Chem. Phys.*, 1934, **2**, 351; cf. Bell, *Trans. Faraday Soc.*, 1931, **27**, 797) by assuming that reagent molecules and transition states can be regarded as electric dipoles immersed in a structureless medium of dielectric constant ε and that all non-electrostatic interactions are unimportant. The figure includes a plot of rate data on benzoyl chloride in acetone–water mixtures which shows that a linear relation of the type mentioned holds for media containing between 15 and ~35% of water by weight. On continuation of the curve to more aqueous media, a departure from linearity appears to set in fairly suddenly. On this basis one would conclude that over the linear portion of the curve the hydrolysis occurs entirely by a single mechanism only, presumably a bimolecular reaction, and that for higher water concentrations a unimolecular mechanism is responsible for part of the rate. One may then attempt to derive from the difference between the experimental points in this region and the extrapolation of the linear portion of the curve (shown as a broken line) values for the unimolecular contribution to the rate. For 50% acetone–water it is thus found that the rate constant for unimolecular hydrolysis (k_1) has a value of $\sim 11 \times 10^{-5}$ sec.$^{-1}$, which is in good agreement with the value derived

from the competition experiments. Internal consistency is given to this analysis by the fact that a plot of the values for log k_1 derived from experiments with different acetone–water mixtures against $(\varepsilon - 1)/(2\varepsilon + 1)$ is linear.

Nevertheless, it should be pointed out that application of this mechanistic criterion to an unknown system does not seem justified until there is more evidence that linear relations of this type are in fact the rule for solvolytic reactions for which it is known from a kinetic analysis that one mechanism alone is important. It was reported earlier (Gold, *loc. cit.*) that the hydrolysis of acetic anhydride in acetone–water is an example of a reaction for which log k is a linear function of $(\varepsilon - 1)/(2\varepsilon + 1)$. It follows from the Figure, where



that curve for the hydrolysis of acetic anhydride is extended by the inclusion of a more recent experimental result (Emery and Gold, *J.*, 1950, **1450**) (at the same time correcting an error in the drawing of the earlier paper), that this conclusion does not seem justified when the more extensive graph is considered. This curvature occurs for regions of the graph for which the bimolecular mechanism is certain to preponderate.

Experimental

Acetone and acetic anhydride were purified as in previous work (Gold and Jefferson, *J.*, 1953, 1409). Benzoyl chloride (" AnalaR ") was used without purification, but the purity was repeatedly checked by chemical analysis (cf. Emery and Gold, *J.*, 1950, 1443), and appropriate corrections were applied for the presence of free acids in the specimens used in kinetic experiments. *o*-Chloroaniline was purified by King and Orton's method (*J.*, 1911, **99**, 1380); *o*-nitroaniline was crystallised from aqueous alcohol.

Rate Measurements with Acetic Anhydride.—The velocity of hydrolysis was determined as previously described (Bafna and Gold, *J.*, 1953, 1406). The course of the disappearance of acetic anhydride in the presence of *o*-chloroaniline was followed by simultaneously withdrawing two samples of the reaction mixture and discharging one into an excess of aniline (*a*) and the other into an excess of standard ammonia solution (*b*) (cf. Caudri, *Rec. Trav. chim.*, 1930, **49**, 1). In order to minimise the loss of acetone from the solvent during the run the sampling procedure was similar to that described by Gold, Hughes, Ingold, and Williams (*J.*, 1950, 2466). Solution (*a*) was titrated with standard sodium hydroxide solution. The acetic anhydride reacts very rapidly with the aniline, with the result that in this titration we determine (i) the acid initially present in the preparation ($\equiv z$); (ii) the acid produced by hydrolysis ($= 2x$); (iii) the acid produced by acetylation of *o*-chloroaniline ($= y$); (iv) the acid produced by acetylation of aniline ($= a_0 - x - y$). The total acid concentration in the sample (*a*) is therefore equal to $(a_0 + x + z)$. To solution (*b*) an excess of standard hydrochloric acid solution was added and then back-titrated potentiometrically with standard sodium hydroxide, a quinhydrone electrode being used. The solution was well diluted with water before titration, and any precipitated amine and anilide were removed by filtration. Delivery into an arresting solution of ammonia produces almost instantaneous hydrolysis of the remaining acetic

anhydride. Hence the amount of standard ammonia solution neutralised is a measure of (i) the acid initially present ($= z$); (ii) the acid produced by hydrolysis up to the time of sampling ($= 2x$); (iii) the acid produced by acetylation of *o*-chloroaniline ($= y$); (iv) the acid produced by the instantaneous hydrolysis of the anhydride after sampling [$= 2(a_0 - x - y)$]. The total of these four sources of acid is ($z + 2a_0 - y$). The difference in the amounts of acid produced in samples (*a*) and (*b*) is equal to $a_0 - x - y$, *i.e.*, the amount of acetic anhydride remaining in the reaction solution at the time of sampling. First-order rate coefficients were evaluated graphically (cf. footnote to Table 1).

Rate Measurements with Benzoyl Chloride.—The measurements on benzoyl chloride summarised in Tables 1 and 4 were obtained by dilatometric observation of the reaction velocity. The dilatometer reservoir consisted of a thin-walled narrow helix of 50 ml. capacity, a design intended to minimise heating effects in strongly exothermic reactions. It was verified by independent chemically-followed runs that the dilatometric observations relate to the two acylation reactions.

The observations on salt and medium effects (Tables 3 and 5) relate to such chemical runs, the experimental method being an adaptation of the aniline–water method used in most of our work on the kinetics of the hydrolysis of acid anhydrides.

Determination of ρ.—The total acidity developed in the solution after completion of the reaction (X_∞) from an initial concentration a_0 of acylating agent was determined by titration of aliquot parts of the solution. Each result is the mean of six determinations. The following relations hold between x_∞, y_∞, a_0, and X_∞, after allowance for the traces of free acid initially present in the acylating agent:

$$X_\infty = 2x_\infty + y_\infty;\ a_0 = x_\infty + y_\infty;$$

and hence

$$(\rho + 1) = a_0/(2a_0 - X_\infty).$$

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Heats of Combustion and Molecular Structure. Part II. The Mean Bond Energy Term for the Carbonyl System in Certain Ketones.*

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[Reprint Order No. 5215.]

The heats of combustion ($-\Delta H_c^0$) of diacetyl, benzil, benzyl methyl ketone, and dibenzyl ketone, together with the corresponding latent heats of evaporation (or sublimation), L_g^{st}, have been determined, and used to derive the mean bond energy terms for the carbonyl system, $\bar{E}$(C=O), in these compounds. The significance of these results is briefly considered.

DURING a thermochemical investigation in 1950, of C–O and C=O compounds, we were requested by Dr. Szwarc to include diacetyl and benzyl methyl ketone. The heats of combustion of these compounds, needed in his kinetic investigations, were accordingly measured and reported to Dr. Szwarc in May 1950. They are now recorded with those for the related substances, benzil and dibenzyl ketone.

EXPERIMENTAL

Materials.—Diacetyl, supplied by Light and Co. Ltd., was dried (CaO) and fractionated to give a product, b. p. 88·5—89·0°/750 mm. This product was again fractionated from anhydrous calcium oxide and a fraction of b. p. 88·0—88·2°/758 mm. was collected. Henderson, Henderson, and Heilbron (*Ber.*, 1914, **47**, 887) give b. p. 87—88°/760 mm.

Benzil, supplied by Towers and Co. Ltd., was recrystallised four times from 90% ethanol. Fine yellow prisms were obtained, m. p. 94·5—94·9° (corr.). Limpricht and Schwanert (*Annalen*, 1868, **145**, 338) give m. p. 95°.

* Part I, *Trans. Faraday Soc.*, in the press.

Benzyl methyl ketone (reagent quality), supplied by British Drug Houses Ltd., was fractionated from pure dry calcium oxide under reduced pressure, the first fraction being rejected. A fraction of b. p. 96·0—96·2°/9 mm. was collected. Rupe, Metzer, and Volger (*Helv. Chim. Acta*, 1925, **8**, 851) give b. p. 98—100°/10 mm.

Dibenzyl ketone. The crude yellow acidic material supplied by Light and Co. Ltd. was dissolved in ether, extracted several times with dilute aqueous sodium carbonate, and washed free from alkali. The ether solution was dried ($MgSO_4$), passed through alumina to remove the yellow colour, and concentrated under reduced pressure, whereafter the dibenzyl ketone crystallised, which recrystallised three times from light petroleum [b. p. 40—60°; previously dried (LiH_2)] as fine colourless needles, m. p. 33·0—33·5°. Stobbe, Russwurm, and Schulz (*Annalen*, 1899, **308**, 175) give m. p. 34—35° As dibenzyl ketone decomposes fairly rapidly, especially when exposed to light and air, the product was pelletted as soon as all the light petroleum had been removed *in vacuo*, over phosphoric oxide.

TABLE 1.†

$m_{(vac.)}$ (g.)	Δ	θ_m	Corr. (fuse) (cal.)	Corr. (HNO_3) (cal.)	Corr. (carbon) (cal.)	E' (cal./deg.)	C (cal./deg.)	$-\Delta U_b$ (kcal./mole)
				Diacetyl. M, 86·09.				
1·2491	2·274°	4·25°	71·8	3·2	2·4	3188	0·9	494·7
1·2664	2·303	4·45	71·8	3·4	1·6	3193	0·9	495·0
1·3060	2·373	4·47	71·8	3·5	1·6	3193	0·9	494·7
				Benzil. M, 210·22.				
0·9801	2·384	4·32	71·8	2·1	0·8	3190	0·5	1615·2
0·9268	2·259	4·25	71·8	2·1	0·8	3188	0·5	1617·3
0·9818	2·383	4·49	71·8	2·4	0·8	3194	0·5	1614·2
0·9843	2·392	4·57	71·8	2·2	—	3195·5	0·5	1616·8
				Benzyl methyl ketone. M, 134·17.				
0·8611	2·338	4·53	71·8	1·5	—	3195	0·6	1152·4
0·9116	2·470	4·49	71·8	1·8	1·6	3194	0·7	1150·7
0·9529	2·584	4·42	71·8	4·2	1·5	3192	0·7	1150·8
0·8776	2·377	4·59	71·8	2·8	0·8	3196	0·6	1150·5
				Dibenzyl ketone. M, 210·26.				
0·8396	2·336	4·43	—	2·2	—	3192·5	0·8	1867·3
0·7643 *	2·404	4·65	808·3	11·5	0·8	3198	0·8	1868·2
0·8415	2·342	4·40	—	2·8	0·8	3192	0·8	1868·4

* Combustion carried out with a gelatin capsule as a container.

† Symbols (see Springall, White, and Cass, *loc. cit.*): $m_{(vac.)}$ is the mass (*in vacuo*) of the sample burnt in the run; $\Delta\theta$ is the corrected temperature rise; θ_m is the mean temperature (Beckmann thermometer); Corr. (fuse), Corr. (HNO_3), and Corr. (carbon) are the corrections to be applied for (i) combustion of the larger fuses used for liquids, (ii) the formation of nitric acid, and (iii) the production of unburnt carbon; E' is the heat capacity of the calorimeter-bomb system (including the fuse correction for solids); C is the isothermal correction (Washburn, *J. Res. Nat. Bur. Stand.*, 1933, **10**, 525), and $-\Delta U_b$ is the decrease in intrinsic energy during the combustion reaction conducted at the actual calorimeter jacket temperature and at 30 atm. initial pressure and is given by:

$$-\Delta U_b = M/m[(E' + C)\Delta\theta - \text{corr. (fuse)} - \text{corr. (HNO}_3\text{)} + \text{corr. (carbon)}] \times 10^{-3} \text{ kcal./mole.}$$

TABLE 2.*

Compound	$-\Delta U_b$ mean (kcal./mole)	Standard deviation ($-\Delta U_b$) (%)	Overall uncertainty interval (%)	Washburn corr. w (kcal./mole)	ΔnRT (kcal./mole)	$-\Delta H_c^0$ (kcal./mole)
Diacetyl	494·8	0·022	0·036	0·3	−0·3	494·8 ± 0·2
Benzil	1615·9	0·043	0·050	1·2	−0·9	1615·6 ± 0·8
Benzyl methyl ketone	1151·1	0·038	0·046	0·7	−1·2	1151·6 ± 0·6
Dibenzyl ketone	1868·0	0·019	0·032	1·1	−1·8	1868·7 ± 0·6

* Symbols: w is the Washburn correction (Washburn, *loc. cit.*) to convert $-\Delta U_b$ into the corresponding $-\Delta U_{298}$ term (at 298° c and 1 atm. initial pressure); Δn is the increase in the number of moles of gas in the reaction; $-\Delta H_c^0$ is the decrease in enthalpy in the combustion reaction at 298° c and 1 atm., the "heat of combustion," and is given by:

$$-\Delta H_c^0 = -\Delta U_b - w - \Delta nRT \text{ (see Springall, White, and Cass, } loc.\ cit.\text{).}$$

Combustion Calorimetry.—The substances were burnt under 30 atm. pressure of oxygen in the Mahler–Cook stainless steel bomb, the temperature changes being recorded by a Beckmann thermometer. The apparatus, experimental procedure, and the method of calculation are described elsewhere (Springall, White, and Cass, *Trans. Faraday Soc.*, in the press). The results are in Table 1.

Estimations of Latent Heat (*Standard State to Vapour*), L_g^{st}.—These were made from vapour pressure–temperature measurements in an apparatus developed from Balston's (*Trans. Faraday Soc.*, 1947, **43**, 54). [We now use the apparatus described by Sanderson, "Vacuum Manipulation of Volatile Compounds," Wiley, New York, 1948, p. 84.] The results obtained were: diacetyl, 8·6; benzil, 20·9; benzyl methyl ketone, 13·2; dibenzyl ketone, 21·3 kcal./mole.

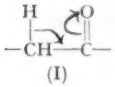
Discussion.

The values of $-\Delta H_c^0$ found for diacetyl and for benzil are considerably lower than the values (503·3 and 1624·6 kcal./mole respectively) reported in Kharasch's compilation (*J. Res. Nat. Bur. Stand.*, 1929, **2**, 359). Results for benzyl methyl ketone and for dibenzyl ketone have not been previously reported. Recent data are available for acetone (Miles and Hunt, *J. Phys. Chem.*, 1941, **45**, 1346) and for ethyl methyl ketone and benzophenone (Parks, Mosley, and Peterson, *J. Chem. Phys.*, 1950, **18**, 152). All these $-\Delta H_c^0$ and the corresponding L_g^{st} terms are listed in Table 3 together with the corresponding mean C:O bond energy terms; $\bar{E}$(C:O) was derived (see Springall, White, and Cass, *loc. cit.*) by using (*a*) the $-\Delta H_f^0$ terms, carbon dioxide 94·05, and water 68·32 kcal./mole, (*b*) the heats of atomisation, ΔH_a, $C_{graphite}$ 171·7, $\frac{1}{2}H_{2(g)}$ 52·09, $\frac{1}{2}O_{2(g)}$ 59·16 kcal./g.-atom (these are the currently accepted "best" values, see, *e.g.*, "Selected Values of Chemical Thermodynamic Properties," Nat. Bur. Stand. Circular 500, Washington, 1952), (*c*) the mean bond energy terms, $\bar{E}$, C–C 83·1, CH:CH (*cis*) 148·2, C–H 98·85 kcal./mole, and (*d*) the resonance energy, E_r, for the C_6H_5–C system 38·9 kcal./mole.

TABLE 3. *Energy term* (*in kcal./mole*).

Compound	$-\Delta H_c^0$	$-\Delta H_f^0$	L_g^{st}	$\bar{E}$(C:O)	Compound	$-\Delta H_c^0$	$-\Delta H_f^0$	L_g^{st}	$\bar{E}$(C:O)
Acetone	427·9	59·2	7·4	179·2	Dibenzyl ketone	1868·7	20·3	21·3	180·5
Ethyl methyl ketone	582·8	66·7	8·3	180·9	Benzophenone ...	1556·4	7·9	20·4	179·5
Benzyl methyl ketone	1151·6	36·45	13·2	178·1	Diacetyl	494·8	86·4	8·6	176·5
					Benzil	1615·6	42·7	20·9	180·8

The general agreement found among the $\bar{E}$(C:O) terms for the monoketonic compounds is good. The mean value, 179·6 kcal./mole, is reasonably concordant with Pauling's value of 152 kcal./mole ("The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, 1940, p. 131) when account is taken of the different values used here for heats of atomisation and the other bond-energy terms.



(I)

With the diketones we feel that the low value of $\bar{E}$(C:O) for diacetyl is significant and is probably due to the suppression of the enol-type hyperconjugation (I) by the mutual polarisation of the adjacent carbonyl groups. No detailed consideration can be given at this stage but the work is being continued.

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The Heats of Formation of Diacetyl and of Benzyl Methyl Ketone in the Vapour Phase.

By G. R. Nicholson, M. Szwarc, and J. Watson Taylor.

[Reprint Order No. 4946.]

The heats of combustion, vaporization, and formation of diacetyl and benzyl methyl ketone have been determined. Special apparatus for purification of the compounds by crystallization has been described and its performance demonstrated on benzene, diacetyl, and benzyl methyl ketone.

Heats of formation, $\Delta H_f(\mathrm{R})$, of free radicals R can be obtained from studies of bond dissociation energies, $D(\mathrm{R{-}R})$, since the heat of formation of a radical R may be obtained from equation (1):

$$\Delta H_f(\mathrm{R}) = \tfrac{1}{2}[D(\mathrm{R{-}R}) + \Delta H_f(\mathrm{R_2})] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

or from equation (2)

$$\Delta H_f(\mathrm{R}) = D(\mathrm{R{-}R'}) + \Delta H\ (\mathrm{RR'}) - \Delta H\ (\mathrm{R'}) \quad . \quad . \quad . \quad . \quad (2)$$

if $\Delta H_f(\mathrm{R'})$ has been determined independently.

Solution of these equations requires a knowledge of the heat of formation of the parent compound, *i.e.*, $\Delta H_f(\mathrm{R_2})$ or $\Delta H_f(\mathrm{RR'})$.

There have been some attempts to determine the dissociation energies $D(\mathrm{MeCO{\cdot}COMe})$ in diacetyl and $D(\mathrm{PhCH_2{\cdot}COMe})$ in benzyl methyl ketone in order to evaluate the heat of formation of the acetyl radical. The heats of combustion of diacetyl and of benzyl methyl ketone were kindly measured in 1950 by Springall and White, at our request. As the figures were much lower than we expected it was decided to repeat the determinations independently, with even more rigorous purification of the compounds and separate determinations of the heats of combustion and vaporization. It will be observed (see Springall and White, preceding paper) that almost identical heats of combustion were obtained.

Experimental

Purification of the Compounds.—(a) *Crystallization apparatus.* The apparatus (Fig. 1) is essentially a container *A* with a sintered-glass plate. An upward stream of dry nitrogen which was passed through the plate supported a liquid above it and ensured efficient mixing of the liquid whose temperature was measured within $\pm 0{\cdot}01°$ by a double-junction copper–constantan thermocouple immersed in it. A cooling-bath *B* enables the rate of cooling to be controlled. When the liquid cooled and had partly crystallized, suction was applied and the mother-liquor collected in the flask below. On rotation of the collecting " pig " through 180° the crystalline material was collected separately after warming. Alternatively the nitrogen stream could be started before the crystals melted and crystallization repeated several times, a small quantity of mother-liquor being removed each time until the material on the sintered plate was sufficiently pure.

The performance of the apparatus was checked by purifying " AnalaR " benzene. Fig. 2 shows the rising m. p. and increasing constancy of the melting temperature. The crystals from the fourth crystallization should be extremely pure, as judged by the almost horizontal direction of the fourth cooling curve, and lack of further increase of the m. p.

(b) *Purification of diacetyl.* Diacetyl was distilled through an 18" × 17 mm. column packed with 1/16" Dixon rings (metal gauze), as supplied by Griffin and Tatlock. The efficiency of the column was estimated at 33 theoretical plates with a carbon tetrachloride–benzene mixture. The fraction collected boiled within 1°. On crystallization as in (a), after the first crystallization of about 80 g. about 20 ml. of mother-liquor were sucked off. Three further crystallizations were made, about 10 ml. of mother-liquor being removed each time. The crystals were then

melted and recrystallized without pre-saturation of the nitrogen stream * and hence without the possibility of reintroducing the impurities. The final crystallization took place within 0·05°. The mother-liquor and crystals from this fifth crystallization were sealed in ampoules.

(c) *Purification of benzyl methyl ketone.* The commercial product supplied by L. Light & Co., Ltd., was converted into its semicarbazone (m. p. 187°; recorded values range between 186° and 194°). The latter was crystallized from hot ethanol, about 50% of the semicarbazone dissolved being collected. The ketone was regenerated by refluxing of the semicarbazone with an excess of 12% sulphuric acid, followed by steam-distillation. The colourless oil obtained was dried, and then distilled in a vacuum through the column described above. The middle fraction (about 60% of charge) was redistilled in a high vacuum out of contact with grease, to remove any grease contamination, and crystallized as above.

The m. p. was −15°. The erroneous value (+27°) is reported in Heilbron's " Dictionary of Organic Compounds."

Heats of Combustion.—Heats of combustion were determined in an isothermal bomb calorimeter apparatus of Dickinson type (*Bull. Bur. Stand.*, 1915, **11**, 189), the calorimeter

FIG. 1.

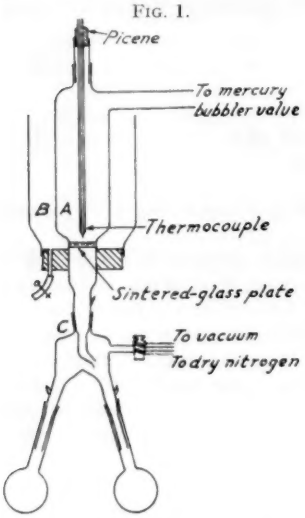
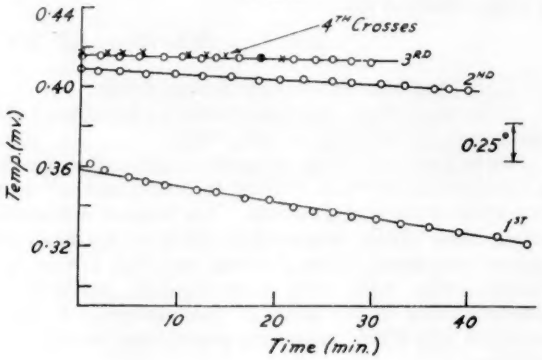


FIG. 2.



having previously been calibrated by combustion of benzoic acid (National Bureau of Standards sample No. 39g). The bomb had a capacity of 540 c.c., and the temperature of the calorimeter was measured by means of a platinum resistance thermometer in conjunction with a Smith's difference bridge. Soda-glass ampoules were completely filled with diacetyl or benzyl methyl ketone by means of a hypodermic syringe, and then sealed. Filled ampoules were pressure tested at 30 atmosphere (equal to the initial oxygen pressure in the bomb), and those surviving were used for combustion. The weight of liquid used, which depended on the size of the individual ampoule, was 1·4—1·7 g. for diacetyl and 1·5—1·8 g. for benzyl methyl ketone. To assist bursting, the ampoules were smeared locally with a small quantity (about 0·02 g.) of petroleum jelly which was ignited by means of a platinum wire and cotton-thread fuse. Corrections to the gross heat evolved were made for the heats of combustion of the cotton and petroleum jelly (previously determined), the joule heat in the platinum wire, and the heat produced in the formation of a small quantity of nitric acid in the bomb from residual nitrogen in the oxygen. Corrections were also made for very small quantities of residual carbon found fused into the remains of the ampoule in a number of combustion experiments. The weights of the samples for combustion were corrected for buoyancy by using measured densities at 20° of 0·973 g./c.c. (diacetyl) and 1·003 g./c.c. (benzyl methyl ketone). The weights were corrected in addition for the measured water content of the samples, *viz.*, 0·084% (diacetyl) and 0·21% (benzyl methyl ketone). Corrected sample weights were converted into moles by using molecular

* In the previous crystallizations the nitrogen stream was pre-saturated with diacetyl vapour to avoid local cooling of the liquid and consequent blocking of the plate.

weights of 86·088 (diacetyl) and 134·170 (benzyl methyl ketone). The molar energy change in the bomb process, U_B, was corrected to the standard heat of combustion at 25° and 1 atm., $\Delta H_c°$, by Washburn's method (*J. Res. Nat. Bur. Stand.*, 1933, **10**, 525). The estimated error in the mean value of $\Delta H_c°$ was calculated by combining the combustion error (twice the standard error of the mean $\Delta H_c°$), the benzoic acid calibration error, and the water content determination error of the sample.

Heats of Vaporization.—The latent heat of vaporization of diacetyl was determined by measurement of its vapour pressure in the range 0—20°, where it lay between about 12 and 39 mm. Pressures of this order could conveniently be measured directly on a mercury manometer. An equation of the form $\log_{10} p = A + B/T$ was fitted by least squares to the set of values obtained for vapour pressure (p mm.) against $1/T$ (°K), and the values of the constants were found to be $A = 8{\cdot}63772$ and $B = -2066{\cdot}09$. From the Clapeyron–Clausius equation the heat of vaporization was therefore $\Delta H_v = (2066{\cdot}09 \times 10^{-3}) \,.\, \boldsymbol{R} \,.\, \ln 10 =$ 9·45 kcal./mole at the mean temperature of the set of measurements, 9·96° c, with a standard error in the slope of the straight line of ±0·22 kcal./mole. In the absence of data on the specific heats of liquid and gaseous diacetyl this value of ΔH_v was corrected to the saturation condition at 25°, on the assumption that $d(\Delta H_v)/dT = -0{\cdot}0136$ kcal. deg.$^{-1}$ mole^{-1}, the mean value for a number of paraffin hydrocarbons of chain length similar to that of diacetyl ("Selected Values of Chemical Thermodynamic Properties," Nat. Bur. Stand., 1949). The additional correction from saturation pressure to 1 atmosphere at 25° is insignificant. The standard latent heat of vaporization at 25° and 1 atm. was thus calculated at be $\Delta H_v° = 9{\cdot}25 \pm 0{\cdot}22$ kcal./mole.

The latent heat of vaporization of benzyl methyl ketone was determined from the observed variation of vapour pressure with temperature in the range 0—55° approximately. A radioactive ionization gauge, of the type described by Downing and Mellen (*Rev. Sci. Instr.*, 1946, **17**, 218) but modified so that it could be heated above ambient temperature, was used. This apparatus gives an ionization current proportional to the vapour pressure of a given compound for pressures up to about 10 mm. Actual vapour pressure need not be known for the purpose of determining latent heats. Four separate sets of measurements were made and the heat of vaporization calculated by the Clapeyron–Clausius equation. Correction to 25° and 1 atm. was made as for diacetyl and the four values of $\Delta H_v°$ obtained gave as mean $12{\cdot}78 \pm 0{\cdot}06$ kcal./mole.

Heats of Formation.—Standard heats of formation (liquid), $\Delta H_f°$ (l), were calculated from the standard heats of combustion $\Delta H_c°$, with the values −94·052 and −68·317 kcal./mole (*op. cit.*) for the heats of formation respectively of carbon dioxide (g) and water (l). The results are as tabulated (1 calorie = 4·1840 absolute joules).

Compound	$-\Delta H_c°$ (kcal./mole)	$\Delta H_f°$ (l) (kcal./mole)
Diacetyl	493·81 = 0·19	−87·35
Benzyl methyl ketone	1151·65 = 0·40	−36·40

Combining these values for the heats of formation in the liquid state with the respective heats of vaporization gives the following standard heats of formation in the vapour phase, $\Delta H_f°$ (g):

Compound	$\Delta H_f°$ (g) (kcal./mole)
Diacetyl	−78·10
Benzyl methyl ketone	−22·62

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Action of Grignard Reagents and Dialkylcadmiums on Alkylquinolinium and Alkylisoquinolinium Salts. A Relation between the Basic Strength of Anions and their Orientation in Nuclear Substitution Reactions.

By WILLIAM BRADLEY and STANLEY JEFFREY.

[Reprint Order No. 5230.]

Previous work on nuclear substitution by anions and other bases in aromatic nitro- and carbonyl compounds has been extended to alkylquinolinium and alkyl*iso*quinolinium salts. In confirmation of Freund's rule all the Grignard reagents studied gave 2-derivatives of 1-alkyl-1 : 2-dihydroquinoline and 1-derivatives of 2-alkyl-1 : 2-dihydro*iso*quinoline. Similar reactions with dialkylcadmiums gave the same results, though more slowly. The factors which lead to 2- or 4-substitution in quinoline and alkylquinolinium salts are discussed.

WHILST it is generally recognized that active anions and primary and secondary amines can react with aromatic systems at positions *ortho* or *para* to nitro- or carbonyl groups (Bradley, *J.*, 1937, 1091), less is known about the factors which determine whether *ortho*- or *para*-substitution will be the more important. With *meso*benzanthrone it has been shown (Bradley and Sutcliffe, *J.*, 1954, 708) that anions which are most active in forming covalent links with carbonyl-carbon, *e.g.*, NH_2^- and R^-, enter the ring mainly *ortho* to the carbonyl group, whilst the less active ones, *e.g.*, NPh_2^- and OH^-, enter mainly or exclusively in the *para*-position.

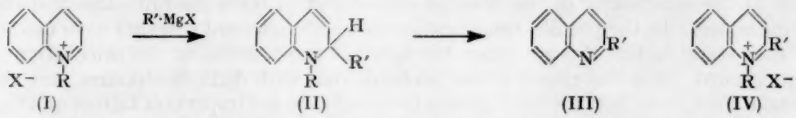
The present investigation is concerned with the same problem in the chemistry of quinoline. 1-Alkylquinolinium salts react with alkali hydroxides and Grignard reagents, to form 1-alkyl-1 : 2-dihydro-2-hydroxyquinolines (Hantzsch and Kalb, *Ber.*, 1899, **32**, 3109) and 1 : 2-dialkyl-1 : 2-dihydroquinolines (Freund, *Ber.*, 1904, **37**, 4666), respectively, whilst alkali cyanides afford 1-alkyl-4-cyano-1 : 4-dihydroquinolines (Kaufmann and Albertini, *Ber.*, 1909, **42**, 3776). These results accord with Bradley and Sutcliffe's work on *meso*benzanthrone, the more active R^- and OH^- anions substituting the quinolinium nucleus at the 2-position whilst the less active CN^- anion combines with the more distant 4-position. Freund (*loc. cit.*) studied the action of methylmagnesium iodide and phenylmagnesium bromide on quinoline methiodide, and Freund and Richard (*Ber.*, 1909, **42**, 1101) studied the action of methylmagnesium iodide on quinaldine methiodide; all the products were 2-substituted 1-alkyl-1 : 2-dihydro-quinolines or -quinaldines. In the present paper a more extended study is described in which both the *N*-substituent and the Grignard reagent have been varied over a wider range with the object of establishing whether 2-substitution is invariable and independent of the size and chemical character of the reacting molecules. Freund and Bode (*ibid.*, p. 1758) showed that Grignard reagents and 2-alkyl*iso*quinolinium salts gave derivatives of 1 : 2-dihydro*iso*quinoline, and this reaction too has been investigated further. Finally, the action of dialkylcadmiums on quaternary salts derived from both quinoline and *iso*quinoline has been studied.

The Grignard Reaction.—The method of experiment was generally the same as that of Freund (*loc. cit.*) but it was standardized and many of the reactions were carried out in duplicate, good agreement being obtained in the results. The Grignard reagents were prepared in ether from an alkyl halide and a slight excess of magnesium, the amount of residual metal being determined and employed to calculate the maximum yields of reagent R·MgX obtained (R = Me, Et, Pr^n, Bu^n, 90—100%; Pr^i, Bu^i, 85%; Bu^s, 80%; Bu^t, 30—35%), which approximate to those reported by Gilman, Zoellner, and Dickey (*J. Amer. Chem. Soc.*, 1929, **51**, 1579) (Et 93, Pr^n 92, Bu^n 94, Pr^i 84, Bu^i 87, Bu^s 78, Bu^t 25%).

In carrying out a reaction 0·2 mole of a qaternary salt was added to 0·3—0·4 mole of a Grignard reagent, except in the case of *tert.*-butylmagnesium bromide where 0·2—0·3 mole of the reagent was used. The yields of 1 : 2-dialkyl-1 : 2-dihydroquinolines obtained are given in Table 1.

All the products were identified as derivatives of 1 : 2-dihydroquinoline (II) by their

decomposition by heat to 2-alkylquinolines (III) (Meisenheimer *et al.*, *Ber.*, 1923, **56**, 1353; 1925, **58**, 2320). In most cases the orientation was confirmed by oxidation with iodine, a 1 : 2-dialkylquinolinium salt (IV) resulting (Kaufmann and Janini, *Ber.*, 1911, **44**,



(I) (II) (III) (IV)

2670). A characteristic feature of all the experiments was the rapidity of the Grignard addition reaction. With any single reagent and a series of alkylquinolinium halides the yield tended to diminish with increase in the size of the alkyl group. All the reactions proceeded to completion and the diminishing yield of isolatable product was due to the formation of emulsions which increased in stability with the size of the alkyl groups and

TABLE 1. *Yields* (%) *of* 1 : 2-*dialkyl*-1 : 2-*dihydroquinoline from* R·MgX *and quinolinium salts.*

Quinoline derivative	R in R·MgX: Me	Et	Pr^n	Pr^i	Bu^n	Bu^i	Bu^s
MeI	85	69	59	45	50	35	45
EtI	75	64	55	42	—	—	—
Pr^{n}I	56	60	53·5	42	50	22	44
	—	—	51	46·5	48	20	44
Pr^{i}I	53·5	50	42	46·5	44	17·5	44

reached a maximum with *sec.*-butyl in the series examined. All the 1 : 2-dialkyl-1 : 2-dihydroquinolines were yellow oils. There was no notable variation in the stability of the dihydro-bases and the yields of 2-alkylquinolines obtained therefrom varied little over the 25 examples examined, except with the *tert.*-butyl compounds, which gave quinoline. Again, on oxidation of the dihydro-bases by alcoholic iodine (Kaufmann and Janini, *loc. cit.*) the related 1 : 2-dialkylquinolinium halides generally resulted, but the *tert.*-butyl compounds lost the *tert.*-butyl group. Because of this the constitution of the dihydro-bases containing *tert.*-butyl groups could not be established, but they were probably 1 : 2-dihydroquinoline derivatives for they had the same order of stability at room temperature as the dihydro-bases containing unbranched alkyl groups; by contrast, the stability of 1 : 4-dihydroquinolines has been stated to be much lower. Quinoline hydriodide gave quinoline with the Grignard reagents from methyl iodide and butyl and *iso*butyl bromide.

The main conclusion from these experiments is that methyl- to butyl-magnesium halides, irrespective of the size and shape of the alkyl group, react with alkylquinolinium salts at the 2-position, in agreement with Freund and Richard's rule.

In a parallel study with 2-alkyl*iso*quinolinium halides reaction occurred readily with all the Grignard reagents investigated, 1 : 2-dialkyl-1 : 2-dihydro*iso*quinolines resulting (see Table 2). Their stabilities at room temperature were similar to those of the corresponding quinoline derivatives. *iso*Quinoline hydriodide gave *iso*quinoline.

TABLE 2. *Yields* (%) *of* 1 : 2-*dialkyl*-1 : 2-*dihydro*isoquinoline *from* R·MgX *and* isoquinolinium *salts.*

*iso*Quinoline derivative	R in R·MgX: Me	Et	Pr^n	*iso*Quinoline derivative	R in R·MgX: Me	Et
MeI	75·5	58	51	Pr^{n}I	56	50
EtI	55	53·5	50	Pr^{i}I	53·5	45

Reaction of 1-*Alkylquinolinium and* 2-*Alkyl*isoquinolinium *Salts with Dialkylcadmiums.*— The reaction of dialkylcadmiums with heterocyclic ammonium salts, which has not been studied previously, was slower than with Grignard reagents and gave more completely isolatable products. These were the same 1 : 2-dihydro-bases that were formed in the Grignard reaction, but because of the lower rate of change it was possible to use the dialkylcadmium reaction to compare the relative rates of substitution by different reagents in various quaternary salts.

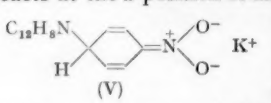
The experiments with *N*-alkyl-quinolinium and *-iso*quinolinium salts, carried out in duplicate, gave the yields shown in Table 3 (for proof of identities see p. 2777). Under standard conditions with any one dialkylcadmium the yield of dihydro-bases fell with increase in the complexity of the *N*-alkyl substituent in both the quinoline and the *iso*-quinoline series. In the parallel investigation in which Grignard reagents were used it was found that steric factors did not affect the speed of the reaction or the orientation of the entering groups. For this reason it was probable that with dialkylcadmiums, too, the size and spatial form as such of the alkyl groups involved were not important factors and that the relative yields were determined by a progressive decrease in the reactivity of the nucleus and of the dialkylcadmium with increase in the complexity of the alkyl groups.

TABLE 3. *Yields* (%) *of* 1 : 2-*dialkyl*-1 : 2-*dihydroquinolines* (*duplicate experiments*) *and* 1 : 2-*dialkyl*isoquinolines.

	R in CdR_2			
	Me	Et	Pr	Pr^i
Quinoline derivative				
MeI	20·1, 19·5 [a]	15·6, 16·2 [b]	8·6, 8·6 [c]	8·0, 8·0
EtI	13·9, 14·5 [e]	9·6, 10·2 [f]	4·4, 4·4 [g]	4·4, 4·0 [h]
PrI	6·4, 7·5 [i]	4·4, 4·4 [k]	Small [l]	Small [m]
Pr^{i}I	5·3, 5·3 [n]	4·0, 4·4 [o]	,, [p]	,, [q]
iso*Quinoline derivative*				
MeI	20·8 [a]	16·2 [b]	9·1 [c]	9·1 [d]
EtI	14·5 [e]	10·7 [f]	5·0 [g]	4·5 [h]
PrI	7·0	4·5 [j]	Small	Small
Pr^{i}I	5·9	4·5 [l]	,,	,,

[a]–[q] See p. 2777.

General Considerations.—The greater nuclear reactivity of the quinolinium cation, compared with that of nitrobenzene and *meso*benzanthrone, is shown by the reaction with aqueous alkali hydroxides and cyanides. On Bradley and Sutcliffe's relation the reaction of the Grignard reagent at the 2-position in a quinolinium cation and the reaction of the cyanide ion at the 4-position is to be expected because the two substituting agents differ widely in reactivity. Similarly both malononitrile and ethyl cyanoacetate react at the 4-position of methylquinolinium iodide (Leonard and Foster, *J. Amer. Chem. Soc.*, 1952, **74**, 2110), and quinaldine methiodide yields an *iso*cyanine (4-substitution) with the same quaternary salt (Mills and Wishart, *J.*, 1920, 579). In Reissert's reaction (*Ber.*, 1905, **38**, 1603) a 1-benzoylquinolinium salt and an alkali cyanide yield a 2-cyano-derivative. In this instance the reactivity of the nucleus has been augmented by the effect of the benzoyl group. The same relation is encountered also in substitutions by a given anion in a series of nuclei. Thus substitution by hydroxyl ions occurs *ortho* in the more reactive quinolinium cation and mainly *para* in the less reactive *meso*benzanthrone. Benzylmagnesium chloride reacts at the 2-position of an alkylquinolinium ion but mainly at the 4-position of pyridine, the nucleus of which is less reactive (Benkeser and Holton, *J. Amer. Chem. Soc.*, 1951, **73**, 5861). Other effects arise from special circumstances. Potassiocarbazole does not react with the quinolinium cation, although reaction takes place easily with nitrobenzene probably because the nitro-group passes into the anion of an *aci*-form with formation of an adduct (V) (Bradley and Robinson, *J.*, 1932, 1254). By contrast the product from potassiocarbazole and an alkylquinolinium salt is a dihydro-base which is incapable of stabilization as an alkali-metal derivative under the conditions employed.



(V)

EXPERIMENTAL

iso*Quinoline* iso*propiodide*, m. p. 174° (from alcohol) (Found: N, 4·7. $C_{12}H_{14}NI$ requires N, 4·5%), resulted (120 g.) when *iso*quinoline (64·5 g.) was heated with *iso*propyl iodide (85 g.) at 100° (sealed tube) for 0·5 hr. The other quaternary salts used in the investigation were prepared by methods recorded in the literature: their purity was checked by analysis. Heating quinoline with *sec.*- or *tert.*-butyl iodide gave only quinoline hydriodide. Similarly with *iso*-

quinoline the two iodides gave only iso*quinoline hydriodide*, m. p. 194° (Found : N, 5·4; I, 48·9. C_9H_8NI requires N, 5·5; I, 49·4%).

Experiments with Potassiocarbazole.—The reagent did not react with quinoline or *iso*quinoline under reflux during 12 hr., or with quinoline or *iso*quinoline ethiodide in quinoline or *iso*quinoline, respectively under (reflux 12 hr.), and in the absence of a solvent (200°, 3 hr.), or with 2-iodoquinoline ethiodide (120—130°, 3 hr.).

Experiments with Sodiofluorene.—No substitution occurred when the reagent (3·7 g.) was heated with quinoline methiodide (5·4 g.) at 150° for 3 hr., or when 1·9 g. was heated with 2-iodoquinoline ethiodide or with 1-iodo*iso*quinoline methiodide (4 g.) at 150° for 3 hr.

Experiments with Piperidine and Morpholine.—Heated under reflux with piperidine (10 c.c.), quinoline methiodide (4 g.) afforded piperidine hydriodide, m. p. 186° (Found : N, 6·5. Calc. for $C_5H_{12}NI$: N, 6·3%). A similar result was obtained when *iso*quinoline methiodide, 2-iodoquinoline ethiodide, and 1-iodo*iso*quinoline methiodide were heated with piperidine. Heated under reflux with morpholine, quinoline methiodide gave morpholine hydriodide, m. p. 215° (Found : N, 6·45. Calc. for $C_4H_{10}ONI$: N, 6·5%). The same salt resulted when *iso*quinoline methiodide, 2-iodoquinoline ethiodide, or 1-iodo*iso*quinoline methiodide was used.

*Experiments with Toluene-*p*-sulphinic Acid.*—There was no reaction when a solution of sodium toluene-*p*-sulphinate (1·78 g.) in water (10 c.c.) was shaken with quinoline or *iso*quinoline ethiodide (2·85 g.) in water (50 c.c.) and ether (50 c.c.).

Experiments with Grignard Reagents.—The reagent was prepared from magnesium (10 g.), alkyl halide (0·4 mole), and ether (250 c.c.), and the resulting solution was decanted from the excess of magnesium when the reaction was complete. The product contained 0·3—0·4 mole of alkylmagnesium halide. In the preparation of *tert.*-butylmagnesium bromide 0·6 mole of *tert.*-butyl bromide and 300 c.c. of ether were used. The yield was 0·2—0·3 mole. In carrying out a reaction the powdered quaternary salt (0·2 mole) was added to the Grignard reagent with stirring. Reaction occurred at once and when it was complete water was added slowly, then hydrochloric acid until two clear layers resulted, and finally ammonium chloride (5 g.) and sufficient ammonia to make the solution alkaline. The ether layer was separated, washed with water (2 × 50 c.c.), and dried for 2 days over solid potassium hydroxide. Evaporation of the ether gave red oils and these were distilled under reduced pressure.

Quinoline methiodide. (*a*) With methylmagnesium iodide the product was a greenish-yellow oil (27 g.), b. p. 70°/0·6 mm. (Found : C, 82·9; H, 8·4; N, 8·8. Calc. for $C_{11}H_{13}N$: C, 83·0; H, 8·2; N, 8·8%) (Freund and Richard, *Ber.*, 1909, **42**, 1101, state b. p. 255—260°). Heated under reflux for 8 hr., the 1 : 2-dihydro-1 : 2-dimethylquinoline (6 g.) gave a greenish-yellow oil (4 g.), b. p. 242—248°, which on redistillation gave quinaldine (3 g.), b. p. 66°/0·4 mm. The derived methiodide, m. p. 193°, did not depress the identical m. p. of quinaldine methiodide.

A solution of the dihydro-base (3 g.) and iodine (4·8 g.) in ethanol (20 c.c.) was refluxed for 15 min. and then cooled. The product which separated crystallised from alcohol, as orange needles, m. p. 193°, not depressed by mixing with quinaldine methiodide.

(*b*) In a similar experiment with ethylmagnesium bromide the yield of 2-ethyl-1 : 2-dihydro-1-methylquinoline (Found : C, 83·0, 83·5; H, 8·8, 8·8; N, 7·8, 7·8. Calc. for $C_{12}H_{15}N$: C, 83·2; H, 8·7; N, 8·1%), b. p. 76—78°/0·5 mm. (Freund and Richard, *loc. cit.*, state b. p. 265°/757 mm., 141—142°/21 mm.), was 24 g. Heating the product (6 g.) under reflux for 10 hr. and distillation gave fractions, (i) b. p. <260°, a yellow oil (4 g.), and (ii) b. p. >260°, an orange-yellow oil (1·6 g.). Redistillation of fraction (i) gave a pale green oil (3 g.), b. p. 72—78°/0·6 mm. (Found : N, 8·5. Calc. for $C_{11}H_{11}N$: N, 8·9%), identified as 2-ethylquinoline by conversion into 2-ethylquinoline methiodide (Found : I, 42·7. Calc. for $C_{12}H_{14}NI$: I, 42·5%), m. p. 166°, not depressed by the authentic compound, m. p. 168°.

On refluxing of the dihydro-base (2 g.) and iodine (2·9 g.) in ethanol (15 c.c.) for 15 min. and cooling, brown crystals, m. p. 142°, separated. Purification from ethanol gave yellow crystals (Found : I, 42·4. Calc. for $C_{12}H_{14}NI$: I, 42·5%), m. p. 168°, and not depressed when mixed with 2-ethylquinoline methiodide.

(*c*) Propylmagnesium bromide gave 22 g. of 1 : 2-dihydro-1-methyl-2-propylquinoline (Found : C, 83·6, 83·6; H, 9·1, 9·4; N, 7·5, 7·3. Calc. for $C_{13}H_{17}N$: C, 83·4; H, 9·1; N, 7·5%), b. p. 96°/0·7 mm. (von Braun and Aust, *loc. cit.*, record 168°/21 mm.; Freund and Kessler, *loc. cit.*, 268—270°; Meisenheimer and Schutze, *Ber.*, 1923, **56**, 1353, b. p. 152°/13 mm.).

Heating of the dihydro-base (5 g.) under reflux for 10 hr. followed by distillation gave as main fraction a light yellow oil, b. p. 276—280° (1·0 g.), and this on fractionation gave 2-propylquinoline (2 g.) (Found : N, 7·9. Calc. for $C_{12}H_{13}N$: N, 8·2%), b. p. 91—93°/1 mm. The methiodide had m. p. 185° (lit., 184°).

A solution of the dihydro-base (7·5 g.) and iodine (10 g.) in ethanol (30 c.c.), heated to boiling and then cooled, gave 2-propylquinoline methiodide (Found: C, 50·0; H, 5·1; N, 4·5; I, 40·4. Calc. for $C_{13}H_{16}NI$: C, 49·8; H, 5·1; N, 4·5; I, 40·6%), m. p. and mixed m. p. 185°.

(*d*) In a similar experiment with *iso*propylmagnesium bromide the yield of 1 : 2-dihydro-1-methyl-2-*iso*propylquinoline, b. p. 90/0·7 mm., was 17 g. (Found: C, 83·7, 83·2; H, 9·3, 9·4; N, 7·7, 7·3. Calc. for $C_{13}H_{17}N$: C, 83·4; H, 9·1; N, 7·5%) (Freund and Kessler, *loc. cit.*, record b. p. 268—274°). After being heated under reflux for 12 hr. the dihydro-base (6 g.) gave a yellow oil (4 g.), b. p. 274—276°, and this gave a fraction, b. p. 74—78°/0·5 mm. (Found: N, 8·4. Calc. for $C_{12}H_{13}N$: N, 8·2%). Union with methyl iodide gave 2-*iso*propylquinoline methiodide, m. p. 190° (lit., 182°). The same compound, m. p. 190°, was obtained from the dialkylcadmium reaction.

With iodine in ethanol the dihydroquinoline (3·7 g.) gave 2-*iso*propylquinoline methiodide (Found: I, 40·6. Calc. for $C_{13}H_{16}NI$: I, 40·6%), m. p. and mixed m. p. 190°.

(*e*) Butylmagnesium bromide gave 20 g. of 2-*butyl*-1 : 2-*dihydro*-1-*methylquinoline*, b. p. 122°/1·5 mm. On redistillation the dihydro-base had b. p. 106—108°/1 mm. (Found: C, 83·1; H, 9·4; N, 7·1. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%).

The dihydro-base (7 g.) decomposed when heated for 12 hr. under reflux. After distillation the main fraction (5 g.) was an orange oil, b. p. 274—290°, and this on redistillation gave a pale green oil, b. p. 94—98°/0·7 mm. (3·5 g.) (Found: C, 84·4; H, 8·3; N, 7·9. Calc. for $C_{13}H_{15}N$: C, 84·3; H, 8·1; N, 7·6%) [Delaby and Hiron (*Compt. rend.*, 1930, **191**, 847) record 153°/14 mm. as the b. p. of 2-butylquinoline]. The picrate had m. p. 162° (*idem*, *ibid.*, m. p. 162°). The *methiodide* crystallised from ethanol as a bright yellow microcrystalline powder, m. p. 175° (Found: C, 51·6; H, 5·7; N, 4·5; I, 38·7. $C_{14}H_{18}NI$ requires C, 51·4; H, 5·5; N, 4·3; I, 38·8%).

With iodine in ethanol 2-butyl-1 : 2-dihydro-1-methylquinoline (8 g.) gave 2-*butylquinoline methiodide*, orange-yellow crystals [from ethanol (charcoal)], m. p. 175° (Found: I, 39·2. $C_{14}H_{18}NI$ requires I, 38·8%), identical with the product prepared from 2-butylquinoline.

(*f*) When *iso*butylmagnesium bromide was used the product was 2-*iso*butyl-1 : 2-dihydro-1-methylquinoline (14 g.) (Found: C, 83·3; H, 9·3; N, 6·6. Calc. for $C_{14}H_{19}N$: C, 83·6; H, 9·5; N, 7·0%), b. p. 98°/0·7 mm. Freund and Kessler (*loc. cit.*) and Meisenheimer, Stotz, and Bauer (*Ber.*, 1925, **58**, 2320) record b. p. 278—280° and 143—144°/12 mm. respectively.

As stated by Meisenheimer *et al.*, the dihydro-base (6 g.), after being heated under reflux for 10 hr. and subsequently distilled, gave a main fraction (2·9 g.), b. p. 274—280° (Found: N, 7·5. Calc. for $C_{13}H_{15}N$: N, 7·6%), as a pale yellow oil, and this combined with methyl iodide to form 2-*iso*butylquinoline methiodide, m. p. 184°. Refluxing with iodine in ethanol converted the dihydro-base into 2-*iso*butylquinoline methiodide. After purification from alcohol (charcoal) this formed bright yellow crystals, m. p. 184° (Found: I, 38·7. Calc. for $C_{14}H_{19}NI$: I, 38·8%), identical with the compound prepared from 2-*iso*butylquinoline.

(*g*) *sec.*-Butylmagnesium bromide afforded 2-sec.-*butyl*-1 : 2-*dihydro*-1-*methylquinoline* (18 g.), b. p. 116°/1·5 mm., 120°/2 mm. (Found: C, 83·5; H, 9·7; N, 6·7. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%). When refluxed for 11 hr. the dihydro-base (7 g.) decomposed and distillation then gave fractions, (i) a pale greenish oil, b. p. 274—280° (0·7 g.), (ii) a yellowish oil, b. p. 280—290° (3·7 g.), and (iii) an orange oil, b. p. 290—300° (9 g.). Redistillation of fraction (ii) gave a pale yellow oil (2·9 g.), b. p. 102—106°/1 mm. (Found: N, 7·3. Calc. for $C_{13}H_{15}N$: N, 7·6%), which formed a picrate, m. p. 163° (Bergstrom, *J. Amer. Chem. Soc.*, 1931, **53**, 4075, records 2-*sec.*-butylquinoline picrate, m. p. 163·5—164·5°). Heating 2-*sec.*-butylquinoline with methyl iodide afforded a dark red viscous mass which solidified after 5—6 days and then crystallised from ethanol (charcoal) as orange-yellow needles of the *methiodide*, m. p. 175° (Found: C, 51·1; H, 5·3; N, 4·2; I, 38·8. $C_{14}H_{18}NI$ requires C, 51·4; H, 5·5; N, 4·3; I, 38·8%).

When the dihydro-base was refluxed with iodine and ethanol 2-*sec.*-butylquinoline methiodide, m. p. 173°, was formed, unchanged by further crystallisations from ethanol (Found: I, 39·3. Calc. for $C_{14}H_{18}NI$: I, 38·8%). It was identical with the salt prepared from 2-*sec.*-butylquinoline.

(*h*) When *tert.*-butylmagnesium bromide was used and the product was distilled, the main fraction (24 g.) was a light yellow oil, b. p. 104°/1·5 mm. (Found: C, 83·6; H, 9·0; N, 6·9. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%). Refluxed for 10 hr. 2-tert.-*butyl*-1 : 2-*dihydro*-1-*methylquinoline* (10 g.) afforded a product from which a main fraction (5 g.) was obtained as a colourless oil, b. p. 230—240°. Redistillation gave 4·6 g., b. p. 80°/2·5 mm. The methiodide, m. p. 132° (Found: I, 46·0. Calc. for $C_{10}H_{10}NI$: I, 46·9%), did not depress the m. p. of quinol-

ine methiodide. The picrate, yellow needles, m. p. 202° (from benzene) was identical with quinoline picrate.

The dihydro-base (4 g.) and picric acid (4·5 g.) were separately dissolved in the minimum volumes of ethanol, and the solutions were mixed. A viscous brown mass separated from the red solution. After collection and washing with cold acetone (6 × 25 c.c.) the yellow solid had m. p. 144°. Repeated crystallisation from water gave yellow slender needles of *1-methylquinolinium picrate*, m. p. 166° (Found: N, 15·0. $C_{16}H_{12}O_7N_4$ requires N, 15·1%).

Quinoline ethiodide. (*a*) Methylmagnesium iodide gave *1-ethyl-1 : 2-dihydro-2-methylquinoline* (26 g.), b. p. 88°/1 mm. (Found: C, 83·5; H, 8·5; N, 7·9. $C_{12}H_{15}N$ requires C, 83·2; H, 8·7; N, 8·1%). When heated under reflux for 10 hr. the dihydro-base (7 g.) gave as main fraction a greenish-yellow oil (4 g.), b. p. 240—250°. Redistillation afforded 3·4 g., b. p. 84—86°/1·7 mm. [methiodide, m. p. 193° (decomp.); quinaldine methiodide has m. p. 193°]. 1-Ethyl-1 : 2-dihydro-2-methylquinoline with iodine in ethanol gave quinaldine ethiodide, m. p. and mixed m. p. 239° (decomp.) (Found: I, 42·2. Calc. for $C_{12}H_{14}NI$: I, 42·5%).

(*b*) Ethylmagnesium bromide gave *1 : 2-diethyl-1 : 2-dihydroquinoline* (24 g.), b. p. 86°/0·7 mm. (Found: C, 83·4; H, 8·9; N, 7·8. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1; N, 7·5%). Refluxing this for 12 hr. and fractionation gave 2-ethylquinoline (3·2 g.), b. p. 76—78°/0·5 mm. (methiodide, m. p. 168°). Dehydrogenation (30 min.) with iodine in ethanol gave 2-ethylquinoline ethiodide, m. p. and mixed m. p. 170° (Found: C, 50·2; H, 4·9; N, 4·7; I, 40·7. Calc. for $C_{13}H_{16}NI$: C, 49·8; H, 5·1; N, 4·5; I, 40·6%).

(*c*) Propylmagnesium bromide gave *1-ethyl-1 : 2-dihydro-2-propylquinoline* (22 g.), a golden-yellow oil, b. p. 112°/1 mm. (Found: C, 83·7; H, 9·6; N, 7·1. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%). When refluxed for 8 hr. and then distilled twice, this gave 2-propylquinoline, b. p. 92°/1 mm. (methiodide, m. p. 185°). Refluxing for 30 min. with iodine in ethanol gave *2-propylquinoline ethiodide*, m. p. 179—180° (Found: I, 39·0. $C_{14}H_{18}NI$ requires I, 38·8%).

(*d*) *iso*Propylmagnesium bromide similarly gave *1-ethyl-1 : 2-dihydro-2-isopropylquinoline* (17 g.), b. p. 98°/0·6 mm. (Found: C, 83·3; H, 9·7; N, 7·0. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%). Refluxed for 10 hr. and then distilled the dihydro-base gave 2-*iso*propylquinoline, b. p. 78°/0·5 mm. (methiodide, m. p. 190°, identical with the salt prepared from 1-methyl-1 : 2-dihydro-2-*iso*propylquinoline and alcoholic iodine, p. 2777).

(*e*) *tert.*-Butylmagnesium bromide gave tert.-*butyl*-1-*ethyl*-1 : 2-*dihydroquinoline* (26 g.), b. p. 106°/0·4 mm. (Found: C, 83·7; H, 9·6; N, 6·6. $C_{15}H_{21}N$ requires C, 83·7; H, 9·8; N, 6·5%). When 10 g. of this were refluxed for 12 hr. and the product was distilled an amber oil (4·8 g.), b. p. 232—240°, and an orange oil (1·2 g.), b. p. 240—248°, were obtained. Redistillation of the larger fraction gave quinoline (4 g.), b. p. 62°/1 mm. (picrate, m. p. 202°; methiodide, m. p. 132°; m. p.s not depressed by authentic samples). When the dihydroquinoline (8·6 g.) was refluxed for 15 min. with iodine (10 g.) in ethanol (25 c.c.) and the resulting solution was cooled a marked odour of *tert.*-butyl iodide was observed. Evaporation afforded a tar and when this was extracted with cold acetone (3 × 20 c.c.) yellow crystals remained. Purification from ethanol gave quinoline ethiodide, m. p. and mixed m. p. 156°.

Quinoline propiodide. (*a*) Methylmagnesium iodide gave *2-methyl-1 : 2-dihydro-1-propylquinoline* (21 g.) as a pale greenish-yellow oil, b. p. 82°/0·4 mm. (Found: C, 83·3; H, 9·3; N, 7·2. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1; N, 7·5%. When heated it gave quinaldine, and when 7·5 g. of the dihydro-base were refluxed for 15 min. with iodine (10 g.) in ethanol quinaldine propiodide resulted. This separated from ethanol as bright yellow crystals, m. p. and mixed m. p. 173° (Found: I, 40·9. Calc. for $C_{13}H_{16}NI$: I, 40·6%).

(*b*) Ethylmagnesium bromide gave *2-ethyl-1 : 2-dihydro-1-propylquinoline* (24 g.), b. p. 100°/0·6 mm. (Found: C, 83·3; H, 8·3; N, 7·1. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%). It yielded 2-ethylquinoline when heated; with iodine in ethanol *2-ethylquinoline propiodide* resulted, which crystallised from ethanol in orange-yellow needles, m. p. 208° (Found: I, 38·7. $C_{14}H_{18}NI$ requires I, 38·8%).

(*c*) Propylmagnesium bromide was used in two independent experiments and the products were separately isolated and analysed. In each case the main fraction, *1 : 2-dihydro-1 : 2-dipropylquinoline*, was a yellow oil: (i) (23 g.) b. p. 102°/0·6 mm. (Found: C, 83·6; H, 9·8; N, 6·6%), (ii) (22 g.) b. p. 114°/1 mm. (Found: C, 83·8; H, 9·9; N, 6·4. $C_{15}H_{21}N$ requires C, 83·7; H, 9·8; N, 6·5%). Heating either preparation gave 2-propylquinoline. The dihydro-base with iodine in ethanol gave *2-propylquinoline propiodide*, bright yellow crystals [from ethanol (charcoal)], m. p. 165—166° (Found: C, 52·8; H, 5·7; N, 4·3; I, 37·1. $C_{15}H_{20}NI$ requires C, 52·8; H, 5·9; N, 4·1; I, 37·2%).

(*d*) Two similar experiments were carried out also with *iso*propylmagnesium bromide. Each

gave 1 : 2-*dihydro*-1-*propyl*-2-iso*propylquinoline* (18 g., 20 g.), b. p. 108°/0·9 mm., 104°/0·7 mm. (Found: C, 83·5, 83·6; H, 9·8, 9·6; N, 6·6, 6·7. $C_{15}H_{21}N$ requires C, 83·7; H, 9·8; N, 6·5%).

Heating gave 2-*iso*propylquinoline, and oxidation with alcoholic iodine gave yellow 2-iso*propylquinoline propiodide*, m. p. 194° (from ethanol) (Found: I, 37·2. $C_{15}H_{20}NI$ requires I, 37·2%).

(*e*) Two experiments with butylmagnesium bromide gave 2-*butyl*-1 : 2-*dihydro*-1-*propylquinoline* (23 g., 22 g.), b. p. 116°/0·7 mm., 136°/1·8 mm. (Found: C, 83·5, 83·7; H, 10·4, 9·8; N, 6·1, 6·4. $C_{16}H_{23}N$ requires C, 83·8; H, 10·0; N, 6·1%). Heating gave 2-butylquinoline. Treatment with iodine gave 2-*butylquinoline propiodide*, m. p. 155—156° (from ethanol) (Found: C, 54·0; H, 6·1; N, 4·0; I, 35·4. $C_{16}H_{22}NI$ requires C, 54·1; H, 6·2; N, 3·9; I, 35·8%).

(*f*) In two similar experiments with *iso*butylmagnesium bromide 2-iso*butyl*-1 : 2-*dihydro*-1-*propylquinoline* was obtained. The main products were yellow oils (10 g., 9 g.), b. p. 104°/0·7 mm., and 100°/0·5 mm. (Found: C, 83·9, 83·9; H, 10·0, 10·1; N, 6·1, 6·1. $C_{16}H_{23}N$ requires C, 83·8; H, 10·0; N, 6·1%). When heated, each gave 2-*iso*butylquinoline, and dehydrogenation with iodine gave 2-iso*butylquinoline propiodide*, m. p. 193° (Found: C, 54·1; H, 6·0; N, 3·7; I, 35·8. $C_{16}H_{22}NI$ requires C, 54·1; H, 6·2; N, 3·9; I, 35·8%).

(*g*) Two experiments with *sec.*-butylmagnesium bromide gave 2-sec.-*butyl*-1 : 2-*dihydro*-1-*propylquinoline* (20 g., 20 g.), b. p. 128°/1·5 mm. (Found: C, 84·0, 83·9; H, 10·5, 10·4; N, 6·1, 6·1. $C_{16}H_{23}N$ requires C, 83·8; H, 10·0; N, 6·1%). It gave 2-*sec.*-butylquinoline when heated. Alcoholic iodine afforded a red tar.

(*h*) Two experiments with *tert.*-butylmagnesium bromide gave a tert.-*butyldihydro*-1-*propylquinoline* (28 g., 27 g.), as a yellow oil, b. p. 100°/0·5 mm. (Found: C, 84·1, 84·0; H, 10·0, 10·1; N, 5·8, 6·1. $C_{16}H_{23}N$ requires C, 83·8; H, 10·0; N, 6·1%). Heated under reflux for 12 hr., dihydro-base (11 g.) gave after redistillation quinoline (4·1 g.), b. p. 72°/2 mm. (picrate, m. p. 202°; methiodide, m. p. 132°; not depressed on admixture with authentic samples). When 9·2 g. of the dihydro-base were refluxed for 15 min. with iodine (10 g.) in ethanol (25 c.c.) the product did not crystallise on cooling, but on addition to ether (75 c.c.) a red tar was precipitated. The solvents were decanted, the residue was kept for 3 weeks and then extracted with cold acetone (3 × 20 c.c.). The solid residue, purified from alcohol, afforded orange-yellow crystals, m. p. 143° (Found: I, 42·8. Calc. for $C_{12}H_{14}NI$: I, 42·5%), of quinoline propiodide.

Quinoline iso*propiodide*. (*a*) Methylmagnesium iodide gave 1 : 2-*dihydro*-2-*methyl*-1-iso*propylquinoline*, a pale greenish-yellow oil (20 g.), b. p. 76°/0·5 mm. (Found: C, 83·7; H, 9·3; N, 7·6. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1; N, 7·5%), and this on heating gave quinaldine. With iodine it gave yellow crystals, m. p. 186°, which on recrystallisation had m. p. 224° (decomp.) (Found: N, 4·7; I, 41·0. Calc. for $C_{13}H_{16}NI$: N, 4·5; I, 40·6%). According to Hamer *et al.* quinaldine *iso*propiodide has m. p. 163·5° (decomp.). The same salt, m. p. 224° (decomp.), was obtained from the dialkylcadmium reaction.

(*b*) Ethylmagnesium bromide gave 2-*ethyl*-1 : 2-*dihydro*-1-iso*propylquinoline* (20 g.), b. p. 90°/0·6 mm. (Found: C, 83·3; H, 9·5; N, 7·2. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%). Heating it gave 2-ethylquinoline. With iodine it gave 2-*ethylquinoline* iso*propiodide*, m. p. 195° (Found: I, 38·9. $C_{14}H_{18}NI$ requires I, 38·8%).

(*c*) Propylmagnesium bromide gave 1 : 2-*dihydro*-2-*propyl*-1-iso*propylquinoline* (18 g.), b. p. 106°/1 mm. (Found: C, 83·7; H, 10·1; N, 6·5. $C_{15}H_{21}N$ requires C, 83·7; H, 9·8; N, 6·5%), which afforded 2-propylquinoline on long heating. Refluxing with iodine in ethanol and then cooling gave a red oil, which partly solidified during 6 weeks; digestion with cold acetone (3 × 20 c.c.) gave a solid, which crystallised from ethanol in orange plates of 2-*propylquinoline* iso*propiodide*, m. p. 174° (Found: N, 3·9. $C_{15}H_{20}NI$ requires N, 4·1%).

(*d*) Similarly, *iso*propylmagnesium bromide gave 1 : 2-*dihydro*-1 : 2-di*iso*propylquinoline (20 g.), b. p. 106°/1·3 mm., 112°/1·5 mm. (Found: C, 83·8; H, 9·9; N, 6·7. $C_{15}H_{21}N$ requires C, 83·7; H, 9·8; N, 6·5%), which gave 2-*iso*propylquinoline on long heating and a tar on oxidation with alcoholic iodine.

(*e*) Butylmagnesium bromide gave 2-*butyl*-1 : 2-*dihydro*-1-iso*propylquinoline* (20 g.), b. p. 106°/0·4 mm. (Found: C, 83·8; H, 10·1; N, 6·0. $C_{16}H_{23}N$ requires C, 83·8; H, 10·0; N, 6·1%). On long heating the dihydro-base gave 2-butylquinoline.

(*f*) *iso*Butylmagnesium bromide gave 2-iso*butyl*-1 : 2-*dihydro*-1-iso*propylquinoline* (8 g.), b. p. 108°/0·7 mm. (Found: C, 84·1; H, 9·9; N, 6·1%), which on long heating gave 2-*iso*butylquinoline.

(*g*) *sec.*-Butylmagnesium bromide gave 2-sec.-*butyl*-1 : 2-*dihydro*-1-iso*propylquinoline* (20 g.), b. p. 104°/0·4 mm. (Found: C, 83·6; H, 10·2; N, 6·4%). 2-*sec.*-Butylquinoline was formed when the dihydro-base was refluxed.

(*h*) *tert.*-Butylmagnesium bromide gave a tert.-*butyldihydro*-1-iso*propylquinoline* (24 g.), b. p. 130°/2·6 mm. (Found: C, 83·5, 83·6; H, 9·8; 10·0; N, 6·2, 6·1%). Refluxing 11 g. of the dihydro-base for 12 hours and distillation of the product gave fractions, (i) b. p. 236—240° (5 g.) and (ii) 248—260° (0·6 g.). Fraction (i) redistilled as a colourless oil, b. p. 78—80°/2·5 mm., which was identified as quinoline by conversion into the picrate and methiodide. Treatment with iodine gave an odour of *tert.*-butyl iodide and a tar which, when stirred with acetone and then crystallised therefrom (charcoal) to constant m. p., formed pale yellow needles, m. p. 98°, not depressed by quinoline *iso*propiodide.

No nuclear substitution was observed in experiments with Grignard reagents and quinoline hydriodide.

Experiments with Quaternary Salts derived from iso*Quinoline*.—These were carried out under the conditions used for the quinoline derivatives. The following substituted 1 : 2-dihydro-*iso*quinolines were obtained: 1 : 2-dimethyl- (24 g.), b. p. 64°/0·3 mm., 76°/1·5 mm. (Found: C, 83·1; H, 8·2; N, 8·8. Calc. for $C_{11}H_{13}N$: C, 83·0; H, 8·2; N, 8·8%) (Freund and Bode, *loc. cit.*, record b. p. 150°/20 mm.); 1-ethyl-2-methyl- (20 g.), b. p. 72°/0·6 mm. (Found: C, 83·6; H, 8·8; N, 7·8. Calc. for $C_{12}H_{15}N$: C, 83·2; H, 8·7; N, 8·1%) (Freund and Bode, *loc. cit.*, record b. p. 165°/45 mm.); 2-*methyl*-1-*propylquinoline* (19 g.), b. p. 84°/0·5 mm. (Found: C, 82·9; H, 9·2; N, 7·4. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1; N, 7·5%); 2-*ethyl*-1-*methyl*- (19 g.), b. p. 74°/0·7 mm. (Found: C, 82·2; H, 9·0; N, 7·7%); 1 : 2-diethyl- (20 g.), b. p. 84°/0·5 mm. (Found: C, 82·8; H, 9·3; N, 7·4. Calc. for $C_{13}H_{17}N$: C, 83·4; H, 9·1; N, 7·5%) (Wedekind and Bandau, *Annalen*, 1913, **401**, 437, record b. p. 145—150°/15 mm.); 2-*ethyl*-1-*propyl*- (20 g.), b. p. 84°/0·3 mm. (Found: C, 83·4; H, 9·5; N, 6·8. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%); 1-*methyl*-2-*propyl*- (21 g.), b. p. 100°/2 mm. (Found: C, 83·2; H, 9·3; N, 7·7%); 1-*ethyl*-2-*propyl*- (20 g.), b. p. 96°/0·5 mm. (Found: C, 83·6; H, 9·7; N, 6·8%); 1-*methyl*-2-iso*propyl*- (20 g.), b. p. 80°/0·5 mm. (Found: C, 83·6; H, 8·9; N, 7·7%); 1-*ethyl*-2-iso*propyl*- (18 g.), b. p. 86—88°/0·6 mm. (Found: C, 83·4; H, 9·5; N, 6·8%).

Experiments with Cadmium Dialkyls.—The cadmium dialkyls were prepared by Gilman and Nelson's method (*Rec. Trav. chim.*, 1936, **55**, 518) and shown to be free from the alkylmagnesium halides from which they were derived. Quinoline methiodide or a similar salt (0·1 mole) was stirred for 4 hr. at the room temperature with an ether solution of the dialkylcadmium (0·2 mole). Water was then added, the precipitate of cadmium hydroxide was removed and washed with ether, and the ether solutions were combined, dried with solid potassium hydroxide, filtered, and evaporated, and the residual red oil was distilled. In all the examples studied distillation occurred at a constant temperature, leaving no residue. The distillates gave 1 : 2-dialkylquinolinium iodides when oxidised with alcoholic iodine. The dihydroquinolines obtained by the dialkylcadmium reaction were identical with those prepared by the use of Grignard reagents. The following notes record briefly the evidence of identity of the products obtained by the Grignard and dialkylcadmium reactions. Reference letters are those in Table 3.

Quinoline series. (*a*) 1 : 2-Dihydro-1 : 2-dimethylquinoline, b. p. 62°/0·4 mm., 74°/0·8 mm. (Found: C, 83·1; H, 8·5; N, 9·0%), was oxidised by iodine to quinaldine methiodide, m. p. 193°. (*b*) 2-Ethyl-1 : 2-dihydro-1-methylquinoline, b. p. 76°/0·5 mm. (Found: C, 83·2; H, 8·8; N, 7·7%), was oxidised to 2-ethylquinoline methiodide, m. p. 168°. (*c*) 1 : 2-Dihydro-1-methyl-2-propylquinoline, b. p. 96°/0·7 mm. (Found: C, 83·7; H, 9·0; N, 7·9%), was oxidised to 2-propylquinoline methiodide, m. p. 185°. (*d*) 1 : 2-Dihydro-1-methyl-2-*iso*propylquinoline, b. p. 90°/0·7 mm. (Found: C, 83·8; H, 8·7; N, 7·3%), was oxidised to 2-*iso*propylquinoline methiodide, m. p. 190°. (*e*) 1-Ethyl-1 : 2-dihydro-2-methylquinoline, b. p. 88°/1 mm. (Found: C, 83·1; H, 8·4; N, 7·9%), gave on oxidation, quinaldine ethiodide, m. p. 239° (decomp.). (*f*) 1 : 2-Diethyl-1 : 2-dihydroquinoline, b. p. 86°/0·7 mm. (Found: C, 83·1; H, 9·5; N, 7·2%), gave 2-ethylquinoline ethiodide, m. p. 170°, on oxidation. (*g*) 1-Ethyl-1 : 2-dihydro-2-propylquinoline, b. p. 104°/0·7 mm. (Found: C, 83·3; H, 9·7; N, 6·8%), gave 2-propylquinoline ethiodide, m. p. 179—180°, on oxidation. (*h*) 1-Ethyl-1 : 2-dihydro-2-*iso*propylquinoline, b. p. 98°/0·6 mm. (Found: C, 83·5; H, 9·5; N, 7·3%), on oxidation with alcoholic iodine gave a tar from which no solid derivative could be prepared. (*i*) 1 : 2-Dihydro-2-methyl-1-propylquinoline, b. p. 84°/0·5 mm. (Found: C, 83·5; H, 9·1; N, 8·0%), gave on oxidation quinaldine propiodide, m. p. 173°. (*k*) 2-Ethyl-1 : 2-dihydro-1-propylquinoline, b. p. 100°/0·6 mm. (Found: C, 83·8; H, 9·6; N, 6·7%), gave 2-ethylquinoline propiodide, m. p. 208°. (*l*) 1 : 2-Dihydro-1 : 2-dipropylquinoline had b. p. 106°/0·7 mm. (Found: C, 83·7; H, 9·9; N, 6·4%). (*m*) 1 : 2-Dihydro-1-propyl-2-*iso*propylquinoline had b. p. 104°/0·7 mm., 100°/0·5 mm. (Found: C, 84·0; H, 9·6; N, 6·5%). (*n*) 1 : 2-Dihydro-2-methyl-1-*iso*propylquinoline, b. p. 76°/0·5 mm. (Found: C, 83·4; H, 9·0; N, 7·8%), on oxidation gave quinaldine

*iso*propiodide, m. p. 224° (decomp.). (*o*) 2-Ethyl-1 : 2-dihydro-1-*iso*propylquinoline, b. p. 90°/0·6 mm. (Found : C, 83·7; H, 9·6; N, 7·1%), gave 2-ethylquinoline *iso*propiodide, m. p. 195°. (*p*) 1 : 2-Dihydro-2-propyl-1-*iso*propylquinoline had b. p. 106°/1 mm. (Found : C, 83·5; H, 9·8; N, 6·4%). (*q*) 1 : 2-Dihydro-1 : 2-di*iso*propylquinoline had b. p. 112°/1·5 mm. (Found : C, 83·8; H, 9·4; N, 6·9%).

iso*Quinoline series.* (*a*) 1 : 2-Dihydro-1 : 2-dimethyl*iso*quinoline had b. p. 68°/1 mm. (Found : C, 83·1; H, 8·1; N, 8·7%). (*b*) 1-Ethyl-1 : 2-dihydro-2-methyl*iso*quinoline had b. p. 76°/0·7 mm. (Found : C, 83·3; H, 8·8; N, 8·2%). (*c*) 1 : 2-Dihydro-2-methyl-1-propyl*iso*quinoline had b. p. 78°/0·4 mm. (Found : C, 83·0; H, 9·4; N, 7·5%). (*d*) 1 : 2-Dihydro-2-methyl-1-*iso*propyl*iso*quinoline had b. p. 86°/0·5 mm. (Found : C, 83·4; H, 9·1; N, 7·6%). (*e*) 2-Ethyl-1 : 2-dihydro-1-methyl*iso*quinoline had b. p. 74°/1 mm. (Found : C, 82·9; H, 8·9; N, 7·9%). (*f*) 1 : 2-Diethyl-1 : 2-dihydro*iso*quinoline had b. p. 84°/0·5 mm. (Found : C, 83·2; H, 9·4; N, 7·4%). (*g*) 2-Ethyl-1 : 2-dihydro-1-propyl*iso*quinoline had b. p. 89°/0·5 mm. (Found : C, 83·6; H, 9·5; N, 6·7%). (*h*) 2-Ethyl-1 : 2-dihydro-1-*iso*propyl*iso*quinoline had b. p. 76°/0·2 mm. (Found : C, 83·3; H, 9·4; N, 7·2%). (*i*) 1 : 2-Dihydro-1-methyl-2-propyl*iso*quinoline had b. p. 104°/2·5 mm. (Found : C, 83·2; H, 9·2; N, 7·4%). (*j*) 1-Ethyl-1 : 2-dihydro-2-propyl*iso*quinoline had b. p. 96°/0·5 mm. (Found : C, 83·6; H, 9·2; N, 7·0%). (*k*) 1 : 2-Dihydro-1-methyl-2-*iso*propyl*iso*quinoline had b. p. 92°/1 mm. (Found : C, 83·6; H, 9·4; N, 7·4%). (*l*) 1-Ethyl-1 : 2-dihydro-2-*iso*propyl*iso*quinoline had b. p. 88°/0·6 mm. (Found : C, 83·6; H, 9·1; N, 7·2%). In other experiments no nuclear substitution was observed when the reagent was sodiofluorene, piperidine, morpholine, or toluene-*p*-sulphinic acid.

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CLOTHWORKERS RESEARCH LABORATORY, UNIVERSITY OF LEEDS. [*Received, March 23rd,* 1954.]

The Reversibility of the Adsorption of Catalyst Poisons. Part III. Adsorption and Desorption of Thionaphthen and Thionaphthol on Platinum.*

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In view of the recent application of desorptive methods to the revival of poisoned metallic catalysts, an exploratory study has been made of the adsorption and desorption of sulphur-containing catalyst poisons on to or from platinum surfaces, and of the displacement of an adsorbed poison from catalyst surfaces by the competitive adsorption of an unsaturated substance or of a second poison. The reversibility of the adsorption of such poisons at room temperature has been demonstrated. Adsorption–time and desorption–time curves show that a considerable period is required for the attainment of adsorption–desorption equilibrium.

ALTHOUGH the adsorption of strong catalyst poisons, such as toxic sulphur compounds, on metallic catalysts has been generally regarded as involving chemisorptive poison-to-catalyst bonds of sufficient strength to render this adsorption substantially irreversible at room temperature, it has been shown in Parts I and II of the present series * (see also *J.*, 1953, 1509) that platinum or other catalysts, previously poisoned with typical catalyst poisons—including thiophen, dimethyl sulphide, dimethylphenylphosphine, dimethylphenylarsine, and toxic metallic ions such as zinc or mercury—can be revived by desorptive methods and, from this revival, a reversible type of adsorption has been inferred although the actual desorption and adsorption processes have not yet been studied. It was found that this revival of a poisoned catalyst can be facilitated by applying a second adsorbate such as an unsaturated substance, which appears to act by displacing and removing the poison by competitive occupation of the active surface : indeed, it has been shown that the washing of a poisoned catalyst with a solvent containing an unsaturated substance constitutes a very simple alternative to the chemical detoxication of the poison (*J.*, 1941, 132; 1945,

* Part I, *J.*, 1952, 4284; Part II, *J.*, 1953, 3153.

204 and succeeding papers) and is applicable to cases of poisoning which cannot be dealt with by chemical treatment.

Little is known, however, of the rates and general kinetics of these adsorption and desorption processes with poisons, or of displacement effects in systems containing also an unsaturated component, the latter type of system being of special interest in connection with the catalytic hydrogenation of a poison-containing, unsaturated substrate. The work described in the present paper has been carried out as an exploratory survey of the above effects in liquid systems containing poisons, as a preliminary to a more detailed examination of the equilibria involved.

Experimental

The platinum black used as the adsorbent was made by alkaline formate reduction of chloroplatinic acid, followed by a stabilisation treatment of the nature to be described in detail in a forthcoming paper. The poison to be adsorbed was applied to this platinum as a solution of known concentration, the progress of the adsorption with time being followed by measuring the fall in the poison concentration of the free phase, from which the suspended platinum had been removed temporarily by centrifuging. This periodic analysis was usually carried out optically, by means of a Unicam spectrophotometer, in which case the small sample required could be quickly re-incorporated with the adsorbing system without appreciable disturbance of the adsorption course, but in some cases the estimation was made catalytically by using the sample as a component of a standard liquid-phase hydrogenation system for which a calibration curve connecting the hydrogenation velocity with the poison content had previously been made.

If the more convenient optical method of analysis is used, and if the adsorption of poison is to be determined in the presence of an unsaturated component, it is necessary to choose a poison having a strong optical absorption at a wave-length at which the unsaturated substance—which is usually present in many times the concentration of the poison—does not absorb. Similar conditions of non-interference apply also to the solvent used.

In the desorption work, the platinum was first allowed to adsorb a known amount of poison, following which the system was diluted by the addition of a known volume of fresh solvent containing no poison; or, to obtain an extreme degree of dilution, the supernatant liquid was removed as completely as possible from the poisoned platinum, by centrifuging and decantation, after which the progressive increase in the poison concentration of the free phase, as a result of desorption of poison from the platinum, was followed analytically as above.

Adsorption and Desorption of β-Thionaphthol.—The system taken consisted of 1 g. of platinum in contact with 25 c.c. of acetic acid containing $7{\cdot}5 \times 10^{-6}$ mole of β-thionaphthol, which was found to be an optically suitable poison, having a peak in its absorption spectrum at 2820 Å. Adsorption was allowed to proceed at 20° in a closed pipette shaken under standardised conditions for 7 hr. by means of a mechanical shaker. In order to obtain clear samples for optical analysis, the shaker was stopped periodically during the run and the adsorption process "frozen" by immediate centrifuging, it having been found by separate experiments that the rate of adsorption in the absence of shaking—namely, on to the centrifuged platinum deposit at the bottom of the reaction vessel—was negligibly small compared with the adsorption velocity on to the dispersed platinum during the vigorous shaking, and that the amount of poison thus adsorbed during the short period required for the analysis was too small to be significant. This was also confirmed by the continuous form of the curve obtained. The progressive increase in the poison adsorbed during the test is shown in curve I of Fig. 1.

In order to study the reverse process, first under conditions of extreme dilution, the run was then interrupted and the reaction vessel centrifuged to deposit the platinum, which contained $5{\cdot}64 \times 10^{-6}$ mole of the poison in the adsorbed state, after which the free phase was decanted as completely as possible and replaced by a further charge of 25 c.c. of acetic acid containing no poison. The course of the subsequent desorption of poison into the free phase under conditions similar to those used for the adsorption is shown in curve II of the Figure. These results establish clearly the reversible nature of the adsorption of the poison.

In a further test, with a system consisting of 30×10^{-6} mole of thionaphthol in 100 c.c. of acetic acid containing 1 g. of platinum, the adsorption was allowed to proceed for 144 hr. with periodic extraction and optical analysis of small samples. After this adsorption, instead of completely replacing the liquid phase with fresh solvent as before, 97·5 c.c. of the clear phase obtained by centrifuging at the end of the adsorption run were removed and replaced by a similar volume of poison-free acetic acid. The system, after this replacement and at the start of the

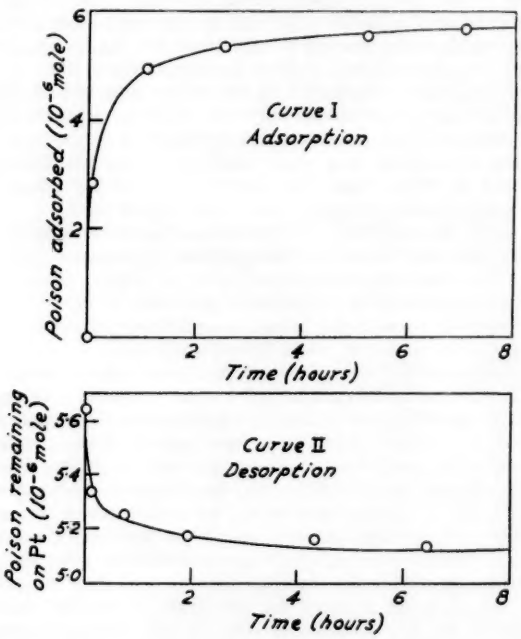
desorption measurements contained $4{\cdot}4 \times 10^{-7}$ mole of poison in the free phase; and, to obtain the amount of poison desorbed after various times, this initial poison content has, of course, to be subtracted from the amounts found analytically. The progress, first of the adsorption and subsequently of the desorption after the dilution, is shown in Table 1.

TABLE 1. *Adsorption and desorption of thionaphthol.*

Adsorption			Subsequent desorption			Adsorption		Subsequent desorption		
Time, hr.	min.	Poison adsorbed (10^{-6} mole)	Time, hr.	min.	Poison desorbed (10^{-6} mole)	Time, hr.	Poison adsorbed (10^{-6} mole)	Time, hr.	min.	Poison desorbed (10^{-6} mole)
	5	2·3		4	1·50	24	6·5	3	12	1·93
	37	2·6		23	1·70	48	8·2	7	2	1·95
1	34	3·5	1	22	1·80	72	10·2			
4	40	4·7	2	31	1·92	144	12·4			

Competitive Occupation of Surface by Poisons and Unsaturated Substances.—A number of examples have been observed of the effectiveness of the competition of an unsaturated substance

FIG. 1.



for the occupation of catalyst surface in the presence of a poison under conditions similar to those operative in an ordinary catalytic hydrogenation system with a poisoned reactant, namely, in which adsorption from a relatively large concentration of a less strongly adsorbed unsaturated substrate competes effectively, by mass action, namely, by virtue of its far greater order of concentration, with the adsorption from a relatively small concentration of the more strongly bonded poison.

Fig. 2 shows the influence of the inclusion, respectively, of 5×10^{-3} (curve *B*) and 10^{-2} (curve *C*) mole of *cyclo*hexene on the adsorption of thionaphthol from ethyl alcohol solution on to 0·1 g. of platinum, the total volume of the liquid system being 10 c.c. and the adsorption being allowed to proceed for a fixed time of 1 hr. in each case. This series was carried out by individual adsorption tests to determine each point, the initial concentration of the poison in the free liquid phase, as shown in the abscissæ, being plotted against the amount of poison adsorbed. Curve *A* represents the corresponding adsorption in the absence of *cyclo*hexene.

It will be seen from the three curves that the depression in the adsorption of the poison by the presence of *cyclo*hexene is very appreciable.

Very similar results were obtained with other poisons. Thus, in a 10 c.c. system containing 40×10^{-7} mole of thionaphthen in acetic acid as the poison, and 0·1 g. of platinum as the adsorbent, the adsorption of poison was 3·55 and $2{\cdot}4 \times 10^{-7}$ mole in the absence and presence, respectively, of 10^{-3} mole of *cyclo*hexene after an adsorption time of 30 min.; or 6·6 and 4·5 units, respectively, after 24 hours' adsorption. A similar depression was also measured for the adsorption of dimethyl sulphide on platinum in alcohol, crotonic acid being used as the unsaturated displacing substance.

Competitive Adsorption of Two Poisons.—If the two poisons in question are reversibly adsorbed, competitive occupation of the catalyst surface takes place in a manner similar to its occupation by a poison and an unsaturated substance: further, it would be expected, on grounds of a greater parity in the adsorption bond strengths, that the displacing effect of adding a second

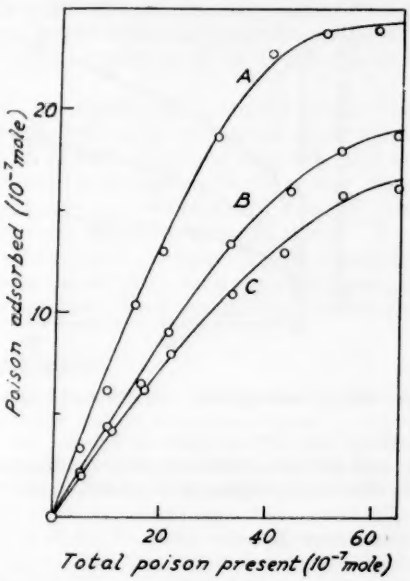


FIG. 2.

A, No *cyclo*hexene.
B, 5×10^{-3} Mole of *cyclo*hexene.
C, 10^{-2} Mole of *cyclo*hexene.

poison to a catalyst already poisoned by a first poison would be more intense than if an unsaturated substance is used as the displacing agent.

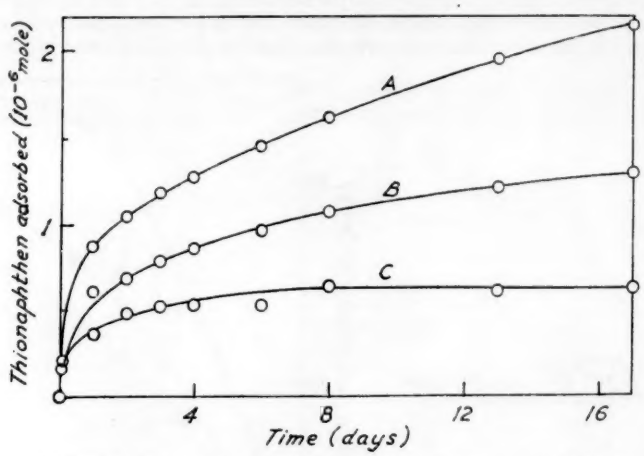
This subject has not yet been studied in detail; but, as an example of the displacement of thionaphthen by thiophen, 1 g. of platinum was allowed to adsorb $11{\cdot}9 \times 10^{-6}$ mole of thionaphthen from acetic acid solution. The poisoned platinum was then separated thoroughly from the supernatant liquid by centrifuging, and treated with $4{\cdot}5 \times 10^{-4}$ mole of thiophen in 25 c.c. of acetic acid. After 24 hr. it was found that this treatment with thiophen had displaced $3{\cdot}75 \times 10^{-6}$ mole, *i.e.*, nearly one-third, of the previously adsorbed thionaphthen from the platinum into the free phase. In this mixed adsorption work, the optical method of analysis has proved to be of great use, since it is necessary to differentiate between the two poisons in a way which cannot be done by the catalytic estimation method. The absorption peaks used were at 2870 Å for thionaphthen and at 2305 Å for thiophen.

This displacement of one poison by another—and especially the substitution, on a poisoned catalyst, of a poison which is easy to deal with by chemical detoxication, in place of one which cannot be detoxicated chemically—might constitute a practical revivification process alternative to poison desorption assisted by an unsaturated substance (Maxted and Ball, *loc. cit.*).

Kinetics of the Adsorption and Desorption of Poisons.—Although the rate both of adsorption and of desorption of poisons is reasonably fast during the first few hours of the process, it is evident that long periods are required for the attainment of equilibrium. This is illustrated in the series of tests shown in Fig. 3, in which the adsorption of thionaphthen from acetic acid

solutions of various initial poison concentrations was followed for 17 days with systems consisting of 0·1 g. of platinum suspended in 10 c.c. of acetic acid containing initially 1, 2, and 8×10^{-6} mole of poison respectively. It will be seen that an approach to a saturated state within the period of the run is obtained only in the lowest of the three runs, namely, that with 10^{-6} mole of thionaphthen: indeed, in this, the adsorption has become very slow and apparently approaches equilibrium after 8 days. The systems were, however, not so vigorously shaken during these very long runs, and the results cannot therefore be directly compared with those of Fig. 1. Moreover, even in the curves of Fig. 1, the adsorption of thionaphthol, after passing through the range shown in curve I, further increased from 5·64 to $6·6 \times 10^{-6}$ mole on extending

FIG. 3.



A, 8×10^{-6} Mole of thionaphthen. *B*, 2×10^{-6} Mole of thionaphthen. *C*, 10^{-6} Mole of thionaphthen.

the adsorption time from 8 hours to 4 days. For this reason, the present adsorption curves cannot be used for an accurate calculation of the equilibrium constant. It is hoped to deal with this, and with the equilibria involved in the adsorption and desorption of poisons, in a later paper.

THE UNIVERSITY, BRISTOL. [*Received, March 20th*, 1954.]

Products from Some Plants of Hong Kong.

By H. R. ARTHUR and (MISS) W. H. HUI.

[Reprint Order No. 5258.]

From the leaves of the following have been isolated: *Eriobotrya japonica*, a mixture of triterpene acids, including ursolic acid, and a little oleanolic acid; *Rhododendron simsii*, ursolic acid and the flavanone matteucinol; *Allamanda cathartica* and *Rhododendron pulchrum*, ursolic acid (the latter plant does not contain matteucinol); *Psidium guaijava*, β-sitosterol.

THE species *Eriobotrya japonica*, Lindl. (loquat), a member of the Rosaceae and one of the common medicinal plants of Hong Kong, is cultivated in the Colony. A decoction of the leaves, and the fruits, are prescribed by herbalists for cough and for nausea. Previous workers have shown that vitamin B_1 and vitamin C are present in the leaves and that ceryl alcohol and ceryl palmitate, and amygdalin, are present in the seeds. In addition to the ursolic acid and oleanolic acid which we have isolated from the leaves of the locally grown species, there occurs another acidic triterpenoid substance which is probably a mixture and is under investigation.

Rhododendron simsii, Planch. (synonyms: *R. Calleryi*, Planch.; *R. balfouria*, Leveille; *R. indicum*, var. *Simsii*, Maxim.), is indigenous to the Colony; *Rhododendron pulchrum*,

Sweet (synonym: *R. phoeniceum*, var. *Smithii*, Wils.) is not. *R. simsii* is reputed to be of medicinal interest. Neither species appears previously to have been investigated, though ursolic acid has been reported in the leaves of *R. hymenanthes* (Kuwada and Matsukawa, *J. Pharm. Soc. Japan*, 1933, **53**, 1065), *R. fauriae* (Kuwaguchi, Kim, and Kim, *ibid.*, 1942, **62**, 4), and *R. linearifolium* (Kariyone and Hashimoto, *ibid.*, 1949, **69**, 313). With our isolation of ursolic acid from the two local *Rhododendrons* the list has been extended to five species and it seems possible that the characteristic triterpene acid of this genus is ursolic acid. Ursolic acid also occurs in other members of the Ericaceae. The isolation of (−)-matteucinol (5 : 7-dihydroxy-6 : 8-dimethylflavanone; S. Fujise, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1929, **11**, 111) which occurs with ursolic acid in the ethereal extract of the leaves of *R. simsii* is interesting since this flavanone has been reported only once previously (from the fern, *Matteucia orientalis*, Munesada, *J. Pharm. Soc. Japan*, 1924, **505**, 185). The leaves of *R. fauriae* (Kuwaguchi *et al.*, *loc. cit.*) contain rhododendrin, the glucoside of rhododendrol, in addition to ursolic acid, and quercetin has been reported from four species of *Rhododendron*, but matteucinol seems to be the first flavanone reported from this genus.

Leaves of *Allamanda cathartica*, Linn. (Apocynaceae), commonly cultivated in the Colony and yielding vitamin C, contain ursolic acid as the only triterpenoid substance.

Psidium guaijava, L. (Myrtaceae), is used in the Colony and elsewhere as a medicinal plant; the leaves are used for throat and chest complaints. Carotene and vitamins B_1, B_2, B_6, and C, and niacin, have been isolated from it. Soliman and Farid (*J.*, 1952, 134) isolated a wax, a phytosterol, and a triterpenoid substance from the leaves. We showed (*J.*, 1954, 1403) that the leaves contained a mixture of triterpene acids (ursolic, oleanolic, crategolic, and guaijavolic). We record here the isolation from the petroleum extract of the leaves β-sitosterol which is presumably the phytosterol isolated by Soliman and Farid (*loc. cit.*).

Experimental

M. p.s are corrected. Analyses are by Dr. Zimmermann, Melbourne. Ursolic acid and oleanolic acid and their derivatives and β-sitosteryl acetate were characterised by mixed m. p. with authentic specimens.

Eriobotrya japonica.—After the dried ground leaves (1 kg.) had been defatted by extraction with light petroleum (b. p. 60—80°) (1 l.) for 4 days at room temperature, they were extracted with ether (2 × 3 l.). The mixed dark green ethereal extracts were shaken with 8% sodium hydroxide solution (2 l.). The green precipitate of crude sodium salts which separated at the interface of the liquids was collected, washed, and then dissolved in hot methanol (charcoal). The solution was acidified; the crude amorphous triterpenoid material which separated on cooling yielded, after 4 crystallisations from ethanol, colourless needles of ursolic acid (5·5 g.), m. p. 289—290°, $[\alpha]_D^{20}$ +64° (*c*, 0·71 in 1 : 1 MeOH–$CHCl_3$) (Found: C, 79·2; H, 10·9%; *M*, 457. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%; *M*, 456). It formed ursolic acid acetate, m. p. 292—294° (Found: C, 76·9; H, 9·9. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%), methyl ursolate, m. p. 168—169° (Found: C, 79·5; H, 10·7; OMe, 6·5. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7; 1OMe, 6·6%), methyl ursolate acetate, m. p. 245—246° (Found: C, 77·8; H, 10·2; OMe, 6·3. Calc. for $C_{33}H_{52}O_4$: C, 77·2; H, 10·2; 1OMe, 6·1%). Methyl ursolate yielded methyl ursonate (prisms from ethanol), m. p. 191—192°, by oxidation with chromic acid (Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555). Ursolic acid gave a red ⟶ violet ⟶ blue ⟶ green colour in the Liebermann–Burchardt test. After removal of 4 crops (ursolic acid) from the ethanolic mother-liquors, the fifth crop on recrystallisation from ethanol yielded colourless needles of oleanolic acid (0·1 g.), m. p. 310—312°. Oleanolic acid was identified by conversion into methyl oleanolate, m. p. 198—200° (Found: C, 78·6; H, 10·7. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%; the supply of oleanolic acid was insufficient for another analysis), and methyl oleanolate acetate, m. p. 220—222°. Oleanolic acid gave a red ⟶ violet ⟶ blue ⟶ green colour in the Liebermann–Burchardt test.

Rhododendron simsii.—Leaves (1 kg.) were extracted with ether (4 l.) and the extract was shaken twice with an equal volume of sodium hydroxide solution (3%). The precipitated sodium salt which formed at the interface was collected, dried, and then dissolved in hot methanol (charcoal). The solution was acidified with concentrated hydrochloric acid. The crude acid separated first as a gel which on recrystallisation from methanol and then ethanol

gave colourless needles of ursolic acid (6 g.), m. p. 289—290° (ursolic acid acetate, m. p. 293—295°; methyl ursolate, m. p. 170°; and methyl ursolate acetate, m. p. 245—246°).

The alkaline extract was filtered through glass wool and the filtrate was immediately acidified. The greenish-yellow precipitate was collected, washed, and recrystallised from methanol (charcoal). Cream-coloured needles separated. Further crystallisation from acetone, methanol, or benzene yielded colourless needles of (−)-matteucinol (4 g.), m. p. 175·5—176°, $[\alpha]_D^{18}$ −30° (*c*, 0·91 in $COMe_2$) (Found: C, 68·9; H, 5·9; OMe, 9·7%; *M*, 312. Calc. for $C_{18}H_{18}O_5$: C, 68·8; H, 5·9; 1OMe, 9·9%; *M*, 314). Matteucinol was soluble in organic solvents and sodium hydroxide solution, and also in warm sodium carbonate solution; it gave a dark olive-green colour with ferric chloride solution in ethanol and a bright red colour with magnesium and hydrochloric acid in ethanol. Matteucinol was identified by the following experiments. (−)-Matteucinol (0·62 g.) was dissolved in aqueous-ethanolic 0·12N-potassium hydroxide (50 ml.). This solution had $[\alpha]_D^{18}$ −36°, then after 2 hr. at room temperature had $[\alpha]_D^{18}$ −30°. When the solution had stood overnight, racemisation was completed by warming for 3 hr. on a steam-bath. The solution was acidified and the precipitate collected and recrystallised several times from methanol. Needles of (±)-matteucinol, m. p. 172·5—173°, were obtained. (±)-Matteucinol was methylated with diazomethane in ether; the product, (±)-7-methoxymatteucinol, which separated from methanol as very pale yellow needles, m. p. 102·5° (Found: C, 69·6; H, 6·0; OMe, 18·7, 18·4%; *M*, 319, 362. Calc. for $C_{19}H_{20}O_5$: C, 69·5; H, 6·2; 2OMe, 18·9%; *M*, 328), was insoluble in dilute sodium hydroxide solution, and gave only a pale colour with ferric chloride solution. (−)-Matteucinol (0·25 g.) was dissolved with fused sodium acetate (0·5 g.) in acetic anhydride (5 ml.). The solution was boiled under reflux for 3½ hr. and poured into water. The precipitate was collected and worked up in the usual manner. The product was crystallised 4 times from ethanol and then 3 times from methanol. Colourless needles of (+)-5 : 7-diacetylmatteucinol, m. p. 169—169·5°, were obtained (Found: C, 66·7; H, 5·6; Ac, 22·0. Calc. for $C_{22}H_{22}O_7$: C, 66·3; H, 5·7; 2Ac, 21·6%); this derivative gave no colour with ferric chloride solution and was insoluble in sodium hydroxide solution.

Rhododendron pulchrum.—Leaves (1 kg.) were extracted with ether (4 l.), and the extract was shaken twice with an equal volume of sodium hydroxide solution (3%). The slight precipitate at the interface was discarded. The alkaline extract was acidified, and the green precipitate of crude ursolic acid was collected, dried, and crystallised from ethanol (charcoal) as needles (1·5 g.), m. p. 289—290°. The acid was converted into the three derivatives described above. No second constituent was obtained from the alkaline extract.

Allamanda cathartica.—The fresh leaves (500 g.) were chopped finely and extracted twice with ether (2 l.). The green ethereal extracts were mixed and worked up by the method stated for *Eriobotrya japonica*. The crude amorphous triterpenoid material (0·7 g.) separated from ethanol as a gel which, after further treatment with that solvent, gave colourless needles of ursolic acid, m. p. 289—291° (identified as ursolic acid acetate, m. p. 293—295°; methyl ursolate, m. p. 168—169°; methyl ursolate acetate, 245—246°). The ethanolic mother-liquors were mixed and concentrated. Several crops of ursolic acid were taken but there was no evidence of the presence of a second constituent.

Psidium guaijava.—The powdered leaves (3 kg.) were extracted with light petroleum (b. p. 60—80°) (10 l.). The extract was concentrated to a dark green gelatinous residue which was diluted with methanol and filtered. The filtrate was concentrated under reduced pressure and distilled with steam. The residue from steam-distillation was boiled under reflux with ethanolic potassium hydroxide for 10 hr., cooled, and extracted with ether. The ethereal solution was dried and distilled, and to the brown residue was added methanol. The rosettes which separated were collected and crystallised from ethanol. The product (0·5 g.), β-sitosterol, separated from ethanol in scintillating plates, m. p. 138—139°, $[\alpha]_D^{21}$ −35° (*c*, 0·2 in chloroform), and gave a red ⟶ violet ⟶ blue ⟶ green colour in the Liebermann–Burchardt reaction. After its reaction with acetic anhydride and pyridine, β-sitosteryl acetate, m. p. 121—122° (Found: C, 81·9; H, 11·3; Ac, 9·8. Calc. for $C_{31}H_{52}O_2$: C, 81·6; H, 11·4; 1Ac, 9·4%), was obtained by working up the product in the usual manner. Crystallisation from methanol of the product obtained from the treatment of β-sitosterol with benzoyl chloride in pyridine yielded β-sitosteryl benzoate, m. p. 144—145°.

The authors thank Professor J. E. Driver for his interest, Mr. H. C. Tang (Government Herbarium, Hong Kong) for identification of plant material, and Professor Th. Bersin (Hausmann Research Laboratory, St. Gallen) for the sample of authentic β-sitosteryl acetate.

UNIVERSITY OF HONG KONG, HONG KONG. [*Received, March 30th*, 1954.]

Organic Oxidation Processes. Part I. The Oxidation of Some Methylphenols with Lead Tetra-acetate.

By G. W. K. Cavill, E. R. Cole, P. T. Gilham, and D. J. McHugh.

[Reprint Order No. 4930.]

The oxidation of phenol, *o*- and *p*-cresol, 2 : 4- and 2 : 6-dimethylphenol, and 2 : 4 : 6-trimethylphenol is described. The " type " products isolated, dihydroxydiphenyls and/or acetoxy*cyclo*hexadienones, vary with (*a*) the solvent effect, (*b*) the proportion of oxidising agent, and (*c*) the position and number of methyl substituents. Mechanisms of oxidation are discussed.

Recently Wessely and his co-workers (*Monatsh.*, 1950, **81**, 1055; 1953, **84**, 425) showed that dehydrogenation with acetoxylation occurs when lead tetra-acetate reacts with a methylphenol in acetic acid solution. Thus *p*-cresol forms 2 : 2-diacetoxy-4-methyl*cyclo*hexadienone (type *A*), the non-aromatic structure being stabilised by the introduction of the acetoxyl groups.

These oxidations were performed in a large excess of acetic acid and such solvent conditions would help, not only to control the instantaneous reaction between substrate and oxidant by high dilution, but, further, to assist in the formation of the monomeric acetoxydienones. The present communication amplifies these investigations, especial attention being paid to solvent influences (cf. Barron, Cavill, Cole, Gilham, and Solomon, *Chem. and Ind.*, 1954, 76). Wessely and Sinwel (*loc. cit.*, 1950) noted the formation of a reddish ether-insoluble solid when benzene was used as solvent for the oxidation of *p*-cresol; it is now shown that, in benzene, lead tetra-acetate favours the formation of dihydroxydiphenyls, particularly when less than molar equivalents are used.

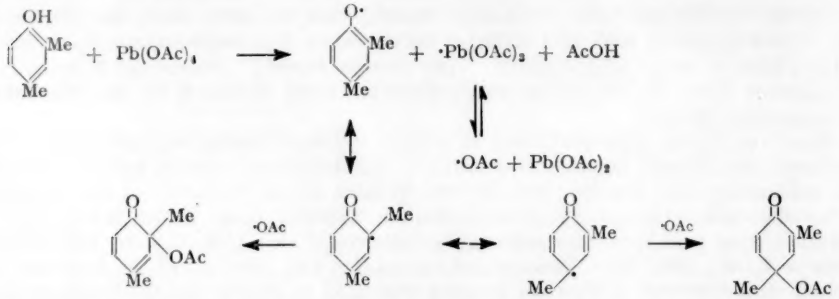
However, the nature of the products is not independent of the structure of the phenol. With increasing *o*- and *p*-substitution by methyl the " type " product isolated changes from a dihydroxydiphenyl (which may appear as a diphenoquinone owing to further oxidation) through mixtures of the dihydroxytetramethyldiphenyls with the corresponding acetoxy*cyclo*hexadienones (from xylenols) until, lastly, mesitol gives only the acetoxydienone. In benzene, the sole product isolated from the oxidation of phenol is 4 : 4′-dihydroxydiphenyl; similarly *o*- and *p*-cresol give a small yield of 4 : 4′-dihydroxy-3 : 3′- and 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl respectively. In acetic acid, no identifiable product could be obtained from the oxidation of phenol; Wessely and Sinwel (*loc. cit.*) obtained 2-acetoxy-2-methyl*cyclo*hexadienone and 2-methyl-1 : 4-benzoquinone from *o*-cresol, and similarly 2 : 2-diacetoxy- and 4-acetoxy-4-methyl*cyclo*hexadienone from *p*-cresol.

Oxidation of 2 : 4-dimethylphenol in benzene affords evidence of two competitive processes. With a 0·5 molar equivalent of the oxidant, the main product is 2 : 2′-dihydroxy-3 : 3′ : 5 : 5′-tetramethyldiphenyl, with some 4-acetoxy-2 : 4-dimethyl*cyclo*hexadienone. With an excess of oxidant, in benzene, the 2-acetoxy-derivative was isolated. From a reaction in acetic acid Wessely and Sinwel obtained a mixture, presumably of the 2- and the 4-acetoxy-compound but isolated only the former in a pure state.

2 : 6-Dimethylphenol, in benzene, readily yields 4 : 4′-dihydroxy-3 : 3′ : 5 : 5′-tetramethyldiphenyl and the corresponding 3 : 3′ : 5 : 5′-tetramethyldiphenoquinone (the quinone is obtained from reaction in acetic acid), but with the oxidant in excess 2 : 6-dimethylbenzoquinone is isolated. The monomeric quinone may have resulted from the further oxidation of the 4-acetoxy*cyclo*hexadienone. Oxidation, in chloroform, gave the diphenoquinone in association with two isomeric compounds, $C_{10}H_{12}O_3$. One of these is proved to be 2-acetoxy-2 : 6-dimethyl*cyclo*hexadienone by reduction to the parent phenol with zinc and acetic acid and by its characteristic ultra-violet absorption spectrum. The second compound has not yet been identified but Wessely and Schinzel (*Monatsh.*, 1953, **84**, 425) have observed the transformation of 2-acetoxy-2 : 4 : 6-trimethyl*cyclo*hexadienone (I) into 4-hydroxy-3 : 5-dimethylbenzyl acetate, and a similar rearrangement may have taken place.

Finally, mesitol, having both the *ortho*- and the *para*-position blocked by methyl groups, yields only the 2-acetoxydienone (I) in chloroform, benzene, or acetic acid.

These results are best explained by a free-radical mechanism involving a stepwise progression to thefinal products. As previously indicated by Pummerer, Melamed, and Puttfarcken (*Ber.*, 1922, **55**, 3116) the initial process is dehydrogenation to a phenoxy-radical and, in support, we note that phenyl acetate does not react with lead tetra-acetate under normal conditions. The nature of the final products isolated then depends on factors which may (*a*) stabilise a mesomeric form of the phenoxy-radical and permit dimerisation, or (*b*) enhance the possibility of acetoxylation and dienone formation. Cordner and Pausacker (*J.*, 1953, 102) and Wessely and Schinzel (*loc. cit.*) postulated similar mechanisms, with which we are in general agreement (see annexed scheme).



Participation of acetate radicals and the free-radical nature of the reaction have been demonstrated by Wessely and his co-workers. Our isolation of the dimeric dihydroxydiphenyls, in benzene, demonstrates the existence of the primary phenoxy-radicals, but oxidations in acetic acid invariably yield acetoxydienones and the formation of such products will be assisted by the propagation of acetate radicals in acetic acid, *viz.* :

$$\cdot Pb(OAc)_3 + AcOH \rightleftharpoons AcOH + \cdot Pb(OAc)_3$$

$$\downarrow\uparrow$$

$$Pb(OAc)_3 + \cdot OAc$$

$$\cdot OAc + AcOH \rightleftharpoons AcOH + \cdot OAc, \text{ etc.}$$

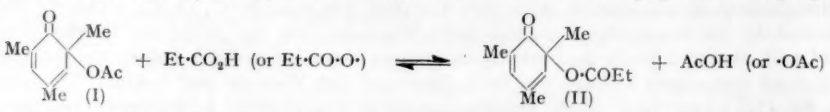
Our isolation of 2 : 4 : 6-trimethyl-2-propionoxy*cyclo*hexadienone (II) from a reaction of mesitol with lead tetra-acetate in propionic acid, and of the 2-acetoxy-compound (I) from an oxidation with lead tetra-propionate in acetic acid, demonstrates that the solvent acid determines the nature of the final acyloxy-derivative. Whether there is (*a*) a radical-transfer process which occurs after initiation of the oxidation reaction :

$$\cdot OAc + Et\cdot CO_2H \text{ (excess)} \rightleftharpoons Et\cdot CO\cdot O\cdot + AcOH$$

(*b*) replacement in the lead tetra-acylate (partial or complete) :

$$Pb(OAc)_4 + Et\cdot CO_2H \text{ (excess)} \rightleftharpoons Pb(O\cdot COEt)_4 + 4AcOH$$

or (*c*) replacement in the final product, *e.g.*, (I ⟶ II), or any combination of the above mechanisms, cannot readily be proved. Related to the third possibility is Wessely and Schinzel's observation (*loc. cit.*) that mesitol, on oxidation with acetyl peroxide in propionic



acid, yields 4-hydroxy-3 : 5-dimethylbenzyl propionate *via* the intermediate acyloxy-dienone (I or II) which was not isolated.

That the oxidation of phenols with lead tetra-acetate is a free-radical process has been confirmed, and solvent effects in such oxidations are fully demonstrated.

Experimental

Light petroleum had b. p. 40—60°.

Oxidation of Phenol.—Phenol (9 g.) in benzene (1 l.) was oxidised with lead tetra-acetate (11 g.), added during 1 hr. Removal of the solvent gave a dark residue from which phenol (6·3 g.) was recovered by steam-distillation. The remaining solid was extracted with hot water (3 × 50 ml.) containing a little acetic acid, and, on cooling, colourless needles of 4 : 4′-dihydroxydiphenyl (0·06 g.) were obtained. Recrystallised from aqueous alcohol these had m. p. and mixed m. p. 265—268° (Found: C, 77·1; H, 5·3. Calc. for $C_{12}H_{10}O_2$: C, 77·4; H, 5·4%). No recognisable product could be isolated from a similar oxidation in acetic acid.

Oxidation of Cresols.—(*a*) *o*-Cresol (5·4 g.) in benzene (100 ml.) was oxidised with lead tetra-acetate (11 g.). The solvent and excess of *o*-cresol were removed in steam, and the residue was treated as for phenol. 4 : 4′-Dihydroxy-3 : 3′-dimethyldiphenyl was finally isolated as colourless prisms (0·05 g.), m. p. and mixed m. p. 156—157°.

(*b*) *p*-Cresol (5·4 g.) in benzene (250 ml.) was oxidised with lead tetra-acetate (11 g.). The mixture, after 2 hr., was treated as above. From the aqueous extracts needles separated, which, after recrystallisation from aqueous alcohol, gave 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (0·4 g.), m. p. and mixed m. p. 153—154° (Found: C, 78·5; H, 6·7. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·6%).

Oxidation of Xylenols.—(*a*) 2 : 4-Dimethylphenol (10 g.) in benzene (150 ml.) was oxidised with lead tetra-acetate (18 g.). The mixture was poured into water and extracted with ether. Fractional distillation gave unchanged phenol (5·0 g.) and a fraction (0·8 g.), b. p. 100—140°/0·05 mm., which in light petroleum yielded 4-*acetoxy*-2 : 4-*dimethyl*cyclo*hexadienone*, m. p. 93—94°, as colourless needles (Found: C, 66·6; H, 6·6. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The ultra-violet absorption spectrum of this compound was analogous to that of 4-acetoxy-derivatives isolated by Wessely and Sinwel (*loc. cit.*). A third fraction (0·7 g.), b. p. 140—160°/0·05 mm., which solidified on cooling, was recrystallised from light petroleum, yielding 2 : 2′-dihydroxy-3 : 3′ : 5 : 5′-tetramethyldiphenyl as colourless prisms, m. p. 133—134° (Found: C, 79·5; H, 7·5. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·5%). Bamberger (*Ber.*, 1907, **40**, 1926) records m. p. 137—138°.

(*b*) 2 : 4-Dimethylphenol (5 g.), oxidised in benzene (200 ml.) with lead tetra-acetate (27 g.), etc., gave 2-acetoxy-2 : 4-dimethyl*cyclo*hexadienone (1·5 g.) as plates, m. p. 69—71° (from light petroleum) (Found: C, 66·5; H, 6·6. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%). Wessely and Sinwel (*loc. cit.*) give m. p. 71·5°.

(*c*) 2 : 6-Dimethylphenol (4 g.) in benzene (200 ml.) was oxidised with lead tetra-acetate (7·3 g.). From the solution crystals were precipitated which were filtered off after addition of water to dissolve lead acetate. This product (0·8 g.), on recrystallisation from acetic acid, gave 3 : 3′ : 5 : 5′-tetramethyl-4 : 4′-diphenoquinone as purplish-red needles, m. p. 205—210° (Found: C, 79·8; H, 6·6. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). Cosgrove and Waters (*J.*, 1951, 388) report m. p. 210—215°. The red benzene layer yielded 4 : 4′-dihydroxy-3 : 3′ : 5 : 5′-tetramethyldiphenyl (0·15 g.) as needles, m. p. 222—223° (from benzene) (Found: C, 79·5; H, 7·4. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·5%). Cosgrove and Waters (*loc. cit.*) report m. p. 221°.

(*d*) 2 : 6-Dimethylphenol (4 g.) in acetic acid (50 ml.) was oxidised with lead tetra-acetate (14·6 g.). The red 3 : 3′ : 5 : 5′-tetramethyl-4 : 4′-diphenoquinone (0·05 g.) was filtered off and recrystallised from acetic acid, as previously described. The residual solution was poured into water and extracted with chloroform. A yellow oil (3·9 g.), b. p. 60—70°/0·1 mm., isolated by fractional distillation, gave 2-*acetoxy*-2 : 6-*dimethyl*cyclo*hexadienone*, prisms, m. p. 35° (from light petroleum) (Found: C, 66·3; H, 6·4. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%), $\lambda_{max.}$ (in EtOH) 305 mμ (cf. ultra-violet absorption spectrum of similar 2-acetoxy-derivatives isolated by Wessely and Sinwel, *loc. cit.*). Reduction of this compound with zinc dust and acetic acid gave 2 : 6-dimethylphenol as needles, m. p. and mixed m. p. 43—45° (from light petroleum).

(*e*) 2 : 6-Dimethylphenol (7·5 g.) in acetic acid (40 ml.) was added dropwise with stirring to a solution of lead tetra-acetate (30 g.) in acetic acid (50 ml.). The oxidant was completely used but under these conditions no diphenoquinone was formed. The chloroform extract gave two fractions on distillation under reduced pressure. The first, which sublimed at 20—40°/0·04 mm., was 2 : 6-dimethyl-*p*-benzoquinone (0·05 g.), recrystallising as yellow needles, m. p.

68—71°, from light petroleum. Noelting and Forel (*Ber.*, 1885, **18**, 2679) give m. p. 72—73°. The second fraction, b. p. 40°/0·04 mm., was chromatographed in light petroleum on alumina to give 2-acetoxy-2 : 6-dimethyl*cyclo*hexadienone, m. p. and mixed m. p. 35°, as previously described.

Oxidation of Mesitol.—(*a*) 2 : 4 : 6-Trimethylphenol (1·4 g.) in benzene (50 ml.) was oxidised with lead tetra-acetate (4·4 g.). The mixture yielded, as above, 2-acetoxy-2 : 4 : 6-trimethyl-*cyclo*hexadienone, colourless needles (1·0 g.), m. p. 84—85° (from light petroleum) (Found : C, 67·8; H, 7·1. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%). Wessely and Sinwel (*loc. cit.*) report m. p. 84°.

(*b*) Mesitol (1·4 g.) in acetic acid (35 ml.) with lead tetra-propionate (5·75 g.) yielded 2-acetoxy-2 : 4 : 6-trimethyl*cyclo*hexadienone (0·45 g.), m. p. and mixed m. p. 83°.

(*c*) Mesitol (1·0 g.) in propionic acid (25 ml.) with lead tetra-acetate (3·6 g.) yielded 2 : 4 : 6-*trimethyl-2-propionoxy*cyclo*hexadienone* as almost colourless plates (0·43 g.), m. p. and mixed m. p. 49—50° (from light petroleum) (Found : C, 68·7; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%), $\lambda_{max.}$ (in EtOH) 311 mμ.

(*d*) Mesitol (2·0 g.) in propionic acid (25 ml.) with lead tetra-propionate (7·1 g.) yielded 2 : 4 : 6-trimethyl-2-propionoxy*cyclo*hexadienone (0·43 g.), m. p. 49—50° (from light petroleum) (Found : C, 69·1; H, 7·6%), $\lambda_{max.}$ (in EtOH) 312 mμ. Catalytic reduction of this compound yielded mesitol, m. p. and mixed m. p. 72°.

Dr. E. Challen is thanked for micro-analyses.

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The Kinetics of the Phenol–Styrene Reaction.

By G. L. FOSTER.

[Reprint Order No. 5144.]

Measurements of the rate of the acid-catalysed addition of styrene to phenol to give *o*- and *p*-1-phenylethylphenols in acetic acid solution at 25° show it to be of the second order. Quantitative theoretical treatment of the relationship between the rate constant and the initial phenol concentration gives good agreement between calculated and observed results. The second-order rate constant is proportional to the acetoxonium-ion concentration, and it is concluded that the acetoxonium ion is the effective catalyst.

THE phenol–styrene reaction was first studied by Koenigs (*Ber.*, 1890, **23**, 3144; 1891, **24**, 3889) using acetic acid as solvent and sulphuric acid as catalyst. He obtained *p*-1-phenylethylphenol, a liquid isomer, and resinous products of higher molecular weight. Stoermer and Kippe (*Ber.*, 1903, **36**, 4012) assumed the liquid isomer to be *o*-1-phenylethylphenol. Pickard and Littlebury (*J.*, 1906, **89**, 469) resolved the compound isolated by Koenigs into its optical isomers by reaction with (−)-menthylcarbimide. The (+)- and the (−)-isomer both melted at 64°. McGreal and Niederl (*J. Amer. Chem. Soc.*, 1935, **57**, 2625) obtained the same compound by condensing 2-phenylethanol with phenol in the presence of zinc chloride and assumed that the alcohol lost water to form styrene which then reacted with phenol. Recently Frisch (*J. Org. Chem.*, 1950, **15**, 587) prepared a number of derivatives of *o*- and *p*-1-phenylethylphenol and Buu Hoï (*J. Org. Chem.*, 1952, 1952, **17**, 243) carried out several condensations closely related to the phenol–styrene reaction.

The overall reaction is summarised by the scheme : $PhOH + CH_2{:}CHPh \longrightarrow$ a mixture of *o*- and *p*-1-phenylethylphenol, but no reaction mechanism based on kinetic measurements has been suggested. Acetic acid was chosen as the solvent because, first it was known from Koenigs's work that the reaction proceeded in that medium at a measurable rate, and secondly there is considerable information available about the properties of acids dissolved in acetic acid; in particular Conant and Hall (*J. Amer. Chem. Soc.*, 1927, **49**, 3047, 3062) studied the strengths of different acids in acetic acid by both electrometric and indicator methods.

In preliminary experiments, sulphuric acid was used as catalyst but, as this was consumed during the reaction, perchloric acid was chosen. There seemed to be less possibility of side reactions between catalyst and reactants with this acid, and Conant and Hall (*loc. cit.*) and Kolthoff and Willman (*J. Amer. Chem. Soc.*, 1934, **56**, 1007) showed that perchloric acid is much more highly ionised than sulphuric acid in acetic acid. The use of a highly-ionised acid is advantageous as it reduces the number of catalytic species present to the solvated proton and the perchlorate ion. An appreciable quantity of un-ionised perchloric acid might also have a catalytic effect, but general acid catalysis is outside the scope of the present research.

Mackenzie and Winter (*Trans. Faraday Soc.*, 1948, **44**, 159) published results of kinetic studies on the acetic acid–acetic anhydride solvent system and included a useful survey of the properties of acids in acetic acid.

Experimental

Acetic acid, of " AnalaR " grade, was distilled to remove unsaturated materials, and dried by the method of Kendall and Gross (*J. Amer. Chem. Soc.*, 1921, **43**, 1428). Alternatively dehydration *in situ* by acetic anhydride proved satisfactory.

Perchloric acid, of " AnalaR " grade 60% aqueous solution, was standardised against " AnalaR " sodium carbonate.

" AnalaR " grade phenol was redistilled, the middle third being kept in a sealed container and exposed to the air for only a few seconds.

Styrene from the Dow Chemical Company, Koppers Co., and Boake Roberts & Co. showed no significant differences. It was freed from inhibitor and distilled under reduced pressure in an inert atmosphere before use.

All materials used in the analysis of reaction samples were " AnalaR " products except technical *cyclo*hexane which was sufficiently pure.

Methods.—For the preparation of the catalyst solution, a weighed quantity of aqueous perchloric acid was washed into a standard flask with acetic acid. Acetic acid was added, followed by the theoretical quantity of " AnalaR " acetic anhydride to react with all the water. The volume was made up with more acetic acid.

The heat of mixing of the perchloric acid and acetic anhydride was regarded as an indication of the rate of dehydration of the catalyst solution by acetic anhydride. Mackenzie and Winter (*loc. cit.*) showed by adding small amounts of water during the Thiele acetylation in acetic anhydride–acetic acid that dehydration is rapid. Dehydration was shown to be complete, by later work in which excess of acetic anhydride was added. The possibility of dehydration to give chlorine heptoxide and acetic acid was considered extremely improbable in view of the very large excess of acetic acid. The solution prepared as described above was stable, and a stock solution (500 ml.) was used for several series.

The catalyst solution was added from a burette to the graduated reaction flask, and solvent was added to the level of the lower of two marks which indicated the amounts of phenol and styrene to be added to give approximately the required initial concentrations. Acetic acid and a little acetic anhydride were added and the mixture kept for at least 4 hr. to ensure dehydration.

The liquid phenol was added from the distillation apparatus to bring the level to the second mark. The reaction mixture was kept for at least 12 hr. to allow the excess of acetic anhydride to react with phenol. The phenyl acetate thus produced would be in small concentration compared with the phenol and styrene, and presumably would not affect the rate constant.

After 12 hr., the reaction was started by adding styrene from a microburette up to the mark, and the first sample for analysis was taken immediately after the homogenising of the mixture. In most experiments, 100 ml. of reaction mixture were prepared.

Traces of water retarded the reaction considerably, and it was impossible to measure formal kinetics until this effect had been studied, and suppressed. Cryoscopic data were obtained on acetic acid–water and acetic acid–acetic anhydride; the cryoscope used was similar to that described by Treffers and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 1708).

A sample of nominally pure acetic acid, m. p. 16·65°, was prepared by the method of Kendall and Gross (*J. Amer. Chem. Soc.*, 1921, **43**, 1428), the product being fractionated and the first third discarded. The effect of the addition of water and acetic anhydride to acetic acid is shown in Fig. 1. In each case, the plot is linear as would be expected.

These cryoscopic measurements were made in conjunction with a series of determinations

to establish the quantitative effect of water and acetic anhydride on the phenol–styrene reaction rate. In all cases the nominally pure fractionated acetic acid was used, and the results are illustrated in Fig. 2 where the second-order rate constants are plotted against the concentration of added water and acetic anhydride, severally. These measurements were made before the quantitative effect of phenol had been studied, but for all points plotted the initial phenol concentration was approximately molar.

Line *A* in Fig. 2 illustrates the sensitivity of the reaction to water. It will be seen that less than 0·1% of water present in the acetic acid is sufficient to reduce the rate constant by half its original value. Other factors being constant, this curve would be governed by the value of K_2 (see equation 2), although there are insufficient results to permit accurate calculation of this constant.

When excess of acetic anhydride was present, as in curve *B*, high and erratic values for the rate constant were obtained. In these experiments, the excess of acetic anhydride was added shortly before the start of reaction, and the erratic values for the rate constant are most probably due to simultaneous styrenation and acetylation of the phenol.

For curve *C* acetic anhydride and phenol were added, and styrene added 12 hr. later to commence the reaction. In these circumstances, the acetic anhydride would react with

FIG. 1. *Cryoscopic measurements on acetic acid/water mixtures and acetic acid/acetic anhydride mixture.*

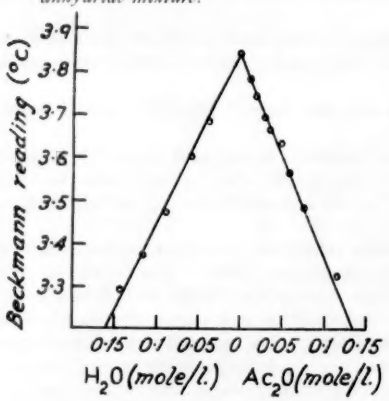
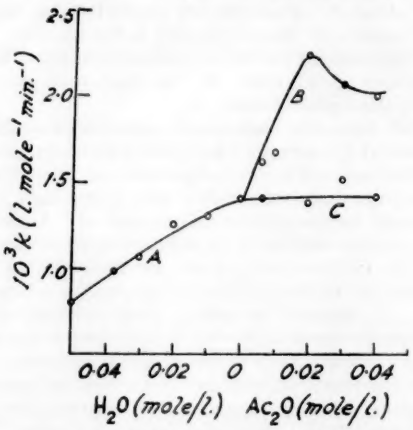


FIG. 2. *Quantitative effect of water and acetic anhydride on second-order rate constant.*



water in the acetic acid, but any acetylation would have ceased before the main reaction commenced. On addition of styrene, the reaction would proceed at a rate similar to that where pure acetic acid alone is used without any addition of anhydride as curve *C* confirms, thus rendering possible a satisfactory method for the *in situ* drying of acetic acid. If fractionated acetic acid was used for a rate determination, a slight excess of acetic anhydride would be added to account for any trace of adventitious water. If the acetic acid was known to have a small water content (calculated from its freezing-point by using Fig. 1) the required amount of acetic anhydride, preferably with a slight excess, would be added with the catalyst. These determinations led to the above standard procedure for initiating the reaction.

Traces of water in the phenol or styrene will not be removed but as the solubility of water in styrene is negligible the styrene never presented any difficulty. Batch variations in phenol, presumably due to traces of water, were observed despite purification.

Provided that the phenol was in considerable excess over the styrene, the further reaction of styrene with the initial products was suppressed, phenol and styrene reacting in equimolar proportions. The rate was determined by measuring the concentration of phenol at different times during reaction.

The styrene was added by volume; a density determination giving the initial concentration. Phenol was determined volumetrically by Koppeschaar's bromide–bromate method as modified by Redman, Weith, and Brook (*Ind. Eng. Chem.*, **1913**, **5**, 389), a little carbon tetrachloride being added to dissolve the flocculent precipitate of tribromophenol which otherwise obscures

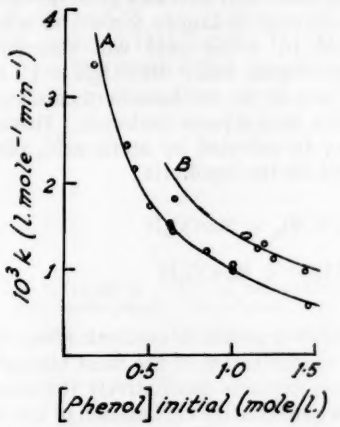
the end point of the titration. The accuracy of the method was confirmed by using a standard solution of phenol in acetic acid.

Since both styrene and the products react with bromine, the phenol was extracted with water and determined in the extract. Acetic and perchloric acids extracted simultaneously are not brominated under these conditions.

The method of sampling and extraction was as follows:

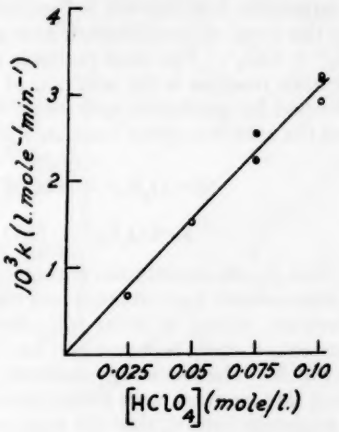
A sample (5 ml.) of reaction mixture was pipetted into a mixture of water (100 ml.) and *cyclo*hexane (75 ml.) in a 250-ml. tap-funnel, and the mixture stirred vigorously for about 10 min. The aqueous layer was removed and the *cyclo*hexane stirred with more water (100 ml.). The phenol in the aqueous extract was then determined. Analysis of mixtures of known composition showed the consistency of the results to be within 1%. The reaction temperature was maintained at 25 ± 0·1°.

FIG. 3. *Variation of second-order rate constant with initial phenol concentration.*



(A), G. & B. *phenol*; (B), B.D.H. *phenol*. Experimental points are shown. The curves are from theoretical calculations (see Discussion).

FIG. 4. *Variation of second-order rate constant with stoicheiometric catalyst concentration.*



Calculation of Results.—The results obeyed the second-order rate equation:

$$k = \frac{2{\cdot}303}{t(a-b)} \log_{10}\left\{\frac{b(a-x)}{a(b-x)}\right\}$$

where a = initial phenol concentration (mole/l.), b = initial styrene concentration (mole/l.), x = mole/l. of phenol consumed at time t (min.), and k = rate constant.

The styrene concentration $(b - x)$ at time t was calulated on the assumption that equimolar concentrations of styrene and phenol react as shown to be reasonable for the part of the reaction studied. In a trial determination, the results obeyed the equation, k being 0·00059 ± 0·00002 l. mole^{-1} min.$^{-1}$ over two-thirds of the reaction.

Dependence on Concentrations of Reagents.—The results of experiments in which the proportions of phenol and styrene were varied to confirm that k was independent of a and b are illustrated in Fig. 3 in which the observed rate constant is plotted against the initial phenol concentration for a range of styrene concentration 0·278—0·416M with the B.D.H. phenol and 0·125—0·424M with the G. and B. phenol. Despite all precautions, there was an inconsistency, which was identified with batch variations in the phenol, but it is concluded that a well-defined relationship exists between the rate constant and the initial phenol concentration although it is not possible to assign a second-order rate constant for the reaction in the ordinary way because of the variation with initial phenol concentration. The purity of the B.D.H. phenol being assumed, the rate constant of the phenol–styrene reaction at 25°, with 0·05M-perchloric acid as catalyst and 1·000M-initial phenol, is 0·00145 ± 0·00007 l. mole^{-1} min.$^{-1}$ which is the highest value obtained within the experimental error. The rate constant is independent of the initial styrene concentration over the ranges studied.

Dependence on Catalyst Concentration.—As shown in the previous section, the effect of varying the stoicheiometric catalyst concentration must be studied at constant initial phenol concentration. This was difficult owing to the method of preparation of the reaction mixture, but of the rate determinations carried out at various perchloric acid concentrations with the same batch of phenol, seven had initial phenol concentrations between 0·82M and 0·87M. Fig. 3 shows that the rate of change of observed rate constant with initial phenol concentration over this range is unlikely to introduce any significant error. Fig. 4 demonstrates the proportionality between rate constant and catalyst concentration up to a concentration of 0·1M-perchloric acid.

Discussion

General Theory and Interpretation of Results.—Kolthoff has shown that the conductivity of perchloric acid in acetic acid solution is not greatly affected by the addition of small amounts of water, whereas the conductivity of sulphuric acid increases greatly when traces of water are added. He concluded that perchloric acid is largely ionised in acetic acid whereas sulphuric acid is not. Perchloric acid in acetic acid will therefore exist largely in the form of acetoxonium ions and perchlorate ions: $Me{\cdot}CO_2H + HClO_4 \rightleftharpoons Me{\cdot}CO_2H_2^+ + ClO_4^-$. The most probable initial step in the mechanism of catalysis of the phenol–styrene reaction is the addition of a proton to a styrene molecule. However the protons formed by perchloric acid ionisation may be solvated by acetic acid, phenol, or water, and the rate of a given reaction will depend on the equilibria:

$$Me{\cdot}CO_2H_2^+ + PhOH \overset{K_1}{\rightleftharpoons} PhOH_2 + Me{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad (1)$$

$$Me{\cdot}CO_2H_2^+ + H_2O \overset{K_2}{\rightleftharpoons} H_3O^+ + Me{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad (2)$$

where K_1 and K_2 are equilibrium constants.

The phenoxonium and oxonium ions may have an appreciable catalytic effect, but even if they have not, phenol or water will affect the concentration of the most strongly acidic species present, namely acetoxonium ion, and this explains qualitatively the relationship shown in Fig. 3. The following treatment gives a quantitative explanation of the variation of observed rate constant with initial phenol concentration. It is assumed that perchloric acid is completely ionised, that the reaction is of the first order with respect to hydrogen-ion concentration, and that constant ionic conditions prevail throughout a given reaction. The third assumption is justified since, although phenol is consumed, it is replaced by another phenol.

If k°, k_p°, and k_o° denote the catalytic constants for acetoxonium, phenoxonium and oxonium ion catalysis, respectively, and h, a^+, and o^+ are their respective concentrations, then the observed second-order rate constant k is given by $k = k^\circ h + k_p^\circ a^+ + k_o^\circ o^+$. By applying the mass law to equations (1) and (2), and treating the acetic acid concentration as constant, we obtain: $a^+ = K_1 ah$ and $o^+ = K_2 oh$.
Thus

$$k = h[k^\circ + k_p^\circ K_1 a + k_o^\circ K_2 o] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If C is the stoicheiometric concentration of perchloric acid and complete ionisation is assumed: $C = h + a^+ + o^+ = h[1 + K_1 a + K_2 o]$
so that

$$h = C/[1 + K_1 a + K_2 o] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Substitution for h in (3) and setting $\gamma_1 = k_p^\circ/k^\circ$ and $\gamma_2 = k_o^\circ/k^\circ$ gives:

$$k = k^\circ C\left[\frac{1 + \gamma_1 K_1 a + \gamma_2 K_2 o}{1 + K_1 a + K_2 o}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

If phenol is the only source of water (as in the present work), $o = c_1 a$, where c_1 is the mole fraction of water in the phenol. Substituting for o in (5) and inverting, we obtain:

$$1/k = \frac{1}{k^\circ C} + \left[\frac{(K_1 + K_2 c_1)a}{k^\circ C}\right]\left[\frac{1}{1 + (\gamma_1 K_1 + \gamma_2 K_2 c_1)a}\right] \quad . \quad . \quad . \quad (6)$$

Now, if phenoxonium and oxonium catalysis are negligible compared with acetoxonium catalysis γ_1 and $\gamma_2 \approx 0$, and k°_p and $k^\circ_o \ll k^\circ$. Thus (6) reduces to the form $1/k = P + Qa$ where $P = 1/k^\circ C$ and $Q = (K_1 + K_2 c_1)/k^\circ C$. The graph of $1/k$ against a should be a straight line of intercept P and gradient Q. P will not be subject to batch variation in the phenol, and from it k° can be calculated; Q depends on the water content of the phenol, but its limiting value, where $c_1 = 0$, gives K_1.

Fig. 5 shows the experimentally observed relationship between $1/k$ and a for two batches of phenol. The linearity demonstrates that phenoxonium and oxonium ion catalysis are not detectable under these conditions and that the effective catalyst is the acetoxonium ion. By using the values for P and Q given by Fig. 5, the curve for the relation between k and a shown in Fig. 3 is calculated.

From Fig. 5, $P = 90$ l.$^{-1}$ mole min. and $C = 0{\cdot}05$ mole l.$^{-1}$, from which $k^\circ = 1/PC = 0{\cdot}22$ l.^{2} mole^{-2} min.$^{-1}$.

If it is assumed that for the B.D.H. phenol $c_1 = 0$, then $Q = K_1/k^\circ C = K_1 P$. The gradient Q for this batch is 614 min. whence $K_1 = 6{\cdot}8$ l. mole^{-1}.

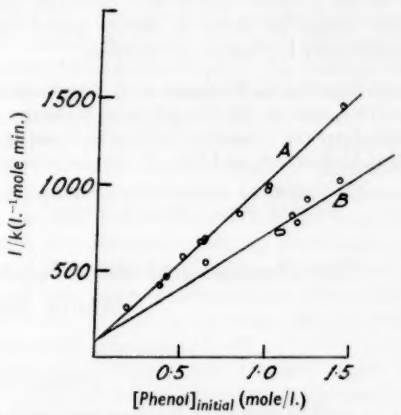


FIG. 5. *Variation of reciprocal rate constant with initial phenol concentration.*
(A), G. & B. *phenol*; (B), B.D.H. *phenol.*

From (6), it will be seen that the rate constant should be proportional to the stoicheiometric catalyst concentration, as demonstrated by Fig. 4. However, since $a^+ = K_1 ah$, and $K_1 = 6{\cdot}8$ l. mole^{-1}, for a molar initial phenol concentration, only about an eighth of the perchloric acid is effective in catalysing the phenol–styrene reaction, even under anhydrous conditions.

In the above treatment it is assumed that the rate of reaction is of first order with respect to each catalytic species present. Since experimental results are in agreement with the theory derived from this assumption, and show k_p° and k_o° to be negligible, the observed rate constant is proportional to the acetoxonium-ion concentration, *i.e.*, $k = k^\circ h$. This being so the mechanism for the reaction suggested is as follows:

$$PhCH{:}CH_2 + Me{\cdot}CO_2H_2^+ \longrightarrow Ph\overset{+}{C}H{\cdot}CH_3 + CH_3{\cdot}CO_2H$$

$$Ph\overset{+}{C}H{\cdot}CH_3 + C_6H_5{\cdot}OH \longrightarrow HO{\cdot}C_6H_4{\cdot}CHPh{\cdot}CH_3 + H^+$$

The mechanism seems more likely than that suggested by Niederl and Natelson (*J. Amer. Chem. Soc.*, 1931, **53**, 272), which involved intermediate ether formation and rearrangement as a general mechanism for the addition of olefins to phenol:

$$RCH{:}CH_2 + H_2SO_4 \longrightarrow RCHMe{\cdot}O{\cdot}SO_3H$$

$$RCHMe{\cdot}O{\cdot}SO_3H + C_6H_5{\cdot}OH \longrightarrow RCHMe{\cdot}O{\cdot}C_6H_5 + H_2SO_4$$

$$RCHMe{\cdot}O{\cdot}C_6H_5 \longrightarrow RCHMe{\cdot}C_6H_4{\cdot}OH$$

The authors used sulphuric acid as catalyst and isolated ethers from the reaction of olefins with phenol at 0°. At higher temperatures substitution occurred, although the ether was relatively stable once formed. Their experiments were not carried out in solution, and therefore the tendency for the sulphuric acid to add on to the olefin was greater than it would be in a solvent such as acetic acid. Even in acetic acid perchloric acid is stronger than sulphuric acid, and any intermediate would be more likely to exist in the form $[R\cdot\overset{+}{C}H\cdot CH_3]ClO_4^-$. The specific case of styrene was not considered by Niederl and Natelson, although 1-phenylethylphenol was obtained from 2-phenylethanol with phenol in the presence of zinc chloride.

The initial step of the mechanism suggested above is similar to that for the ionic polymerisation of styrene. Styrene polymerisation, like the styrene–phenol reaction, can be catalysed by Friedel–Crafts catalysts (Williams, *J.*, 1938, 246, 1046; 1940, 775; 1954, 357; see also Pepper, *Quart. Reviews*, 1954, **8**, 88), and the mechanism of similar ionic polymerisations has been the subject of considerable attention in recent years (Plesch "Cationic Polymerisation and Related Complexes," Heffer, Cambridge 1953, p. 70). In view of the present theory it is probable that the phenol–styrene reaction in acetic acid solution could be used to study under controlled ionic conditions the Friedel–Crafts catalysed polymerisation of styrene.

I am indebted to Professor E. A. Guggenheim, F.R.S., who directed the work, for his interest and advice, and to Professor Gwyn Williams and Dr. E. R. S. Winter for helpful discussion. I thank Imperial Chemical Industries Limited, Paints Division, for the facilities provided at Reading University, and Miss P. Naylor who assisted in the analysis of samples.

Imperial Chemical Industries Limited, Paints Division,
Wexham Road, Slough, Bucks. [*Received, February 22nd*, 1954.]

The Chemistry of the "Insoluble Red" Woods. Part VI. Santalin and Santarubin.*

By Alexander Robertson and W. B. Whalley.

[Reprint Order No. 5250.]

The optically inactive colouring matters santalin, $C_{27}H_{15}O_6(OMe)_3$, and santarubin, $C_{27}H_{14}O_5(OMe)_4$, have been isolated from commercial camwood and barwood and shown to be quinonoid anhydrobenzopyranol bases, devoid of *C*-methyl or reactive carbonyl groups and forming salts by the addition of acids. Sandalwood contains santalin but no santarubin.

Methylation of santalin gave *O*-tetramethylsantalin, a quinonoid anhydro-base, forming salts additively, and *O*-pentamethylsantalin, a benzopyranol. Similarly, santarubin gave *O*-trimethylsantarubin, an anhydro-base, and *O*-tetramethylsantarubin, a benzopyranol. On hydrolytic fission *O*-tetramethylsantalin and *O*-trimethylsantarubin furnished 2 : 4-dihydroxy-5-methoxybenzaldehyde whilst on oxidation *O*-tetramethylsantalin gave rise to veratraldehyde, veratric acid, and 2 : 4-dimethoxybenzoic acid, and *O*-trimethylsantarubin to 2 : 4-dimethoxybenzaldehyde, 2 : 4-dimethoxybenzoic acid, and probably veratric acid. From this evidence provisional structures (VII) and (XI) have been deduced, respectively, for *O*-tetramethylsantalin and *O*-trimethylsantarubin, and it appears that santalin and santarubin are ethers of two isomeric quinonoid anhydro-bases.

The pigments present in commercial specimens of the "insoluble red" woods, sandalwood, camwood, and barwood, have been examined by various investigators, of whom Pelletier (*Annalen*, 1833, **6**, 28) appears to have been the first to obtained a crude preparation to which he assigned the empirical formula $C_{16}H_{16}O_3$ and the name, santalin. By various and often tedious and complicated processes a succession of later investigators (*inter al.*, Preisser, *Berz. Jahresber.*, 1845, **24**, 515; Meier, *Arch. Pharm.*, 1848, **55**, 285;

* Part V, *J.*, 1954, 1440.

1848, **56**, 41; Bolley, *Annalen*, 1847, **62**, 150; Weyermann and Häffely, *ibid.*, 1850, **74**, 226; Anderson, *J.*, 1876, **30**, 582; Franchimont, *Ber.*, 1879, **12**, 14; and Perkin, *J.*, 1899, **75**, 443) isolated crude amorphous pigment fractions, some of which may or may not have been identical with santalin. A crystalline santalin, m. p. 226°, appears to have been first isolated by Cain and Simonsen (*J.*, 1912, **101**, 1061) who obtained it by a complex procedure and ascribed to it the empirical formula $C_{14}H_{11}O_4 \cdot OMe$, which, in collaboration with Smith (*J.*, 1914, **105**, 1335), they subsequently revised to $C_{28}H_{22}O_8(OMe)_2$. By methylation with potassium hydroxide solution and methyl sulphate these authors prepared an *O*-dimethylsantalin, m. p. 165—167° (Found: C, 67·9; H, 6·1; OMe, 31·6%), giving veratric and anisic acid on oxidation. O'Neill and Perkin (*J.*, 1918, **113**, 125) maintained, however, that their microcrystalline santalin had the formula $C_{22}H_{18}O_6(OMe)_2$, and also claimed to have isolated an *iso*santalin, $C_{24}H_{24}O_8$, as a chocolate-coloured powder, which furnished oxonium salts. This was the first indication that these pigments might be benzopyranols or anhydrobenzopyranols.

By the oxidation of santalin (a microcrystalline powder) with alkaline ferricyanide Dieterle and Stegemann (*Arch. Pharm.*, 1926, **264**, 1) claimed the production of homopterocarpin (Part I, *J.*, 1940, 787) but their results were inconclusive and it seems likely that, as the authors themselves appeared to suspect, the homopterocarpin was probably contained as an impurity in their so-called santalin. The first clear recognition of the benzopyranol, or anhydrobenzopyranol, character of santalin is due to Raudintz, Navratil, and Benda (*Ber.*, 1934, **67**, 1036) who proposed the empirical formula $C_{34}H_{23}O_{10}$ for the base.

In our investigations on the colouring matters of the "insoluble-red" woods we extracted the sawdusts of the commercial woods with boiling carbon tetrachloride (cf. Part I, *loc. cit.*) to remove homopterocarpin, pterocarpin, traces of santal (Part III, *J.*, 1949, 1571), and vegetable oils. On subsequent concentration the extracts from camwood and barwood deposited small quantities of a pigment which on purification was obtained in chocolate-coloured prisms. Although this colouring matter, which does not appear to occur in our specimen of sandalwood, resembles somewhat the *iso*santalin of O'Neill and Perkin (*loc. cit.*) we propose, for the sake of clarity, to name the compound santarubin.

After the separation of the santarubin-containing fraction the residual wood was exhausted with ether or chloroform and ultimately a vermilion-coloured pigment was isolated which possibly is identical with the product previously designated santalin and for which we propose to retain this name.

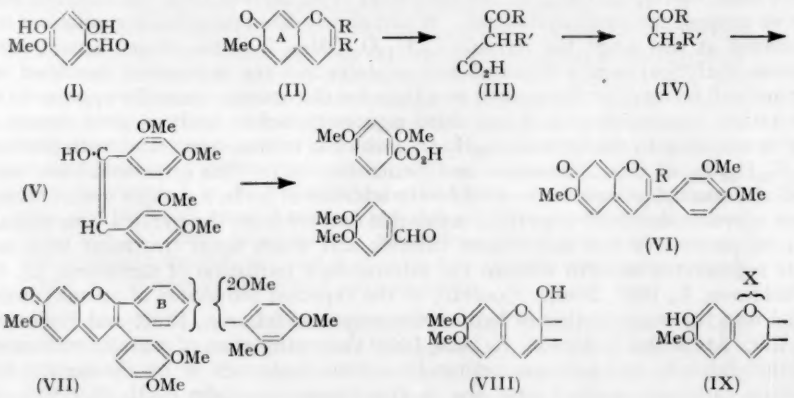
Thus isolated, santalin, m. p. 305° (decomp.), has the properties of an anhydrobenzopyranol base, $C_{27}H_{15}O_6(OMe)_3$, of the quinonoid type, derived from the carbinol base for which we propose the name santalanol. Whilst closely allied empirical formulations cannot be excluded at this stage, the formula $C_{27}H_{15}O_6(OMe)_3$ is in the closest accord with the numerous analytical results obtained with santalin and the derivatives described in this paper and will be used for the present as a basis for discussion. Santalin appears to retain water rather tenaciously and if not dried rigorously before analysis gives results more nearly in accord with the formula $C_{30}H_{26}O_{10}$, which is in close agreement with the formulation $C_{30}H_{28}O_{10}$ of Cain, Simonsen, and Smith (*loc. cit.*). This quinonoid base, which is devoid of *C*-methyl groups, forms salts by the addition of acids, *e.g.*, with hydrochloric acid it gives a hydrochloride of type (IX), a chloride derived from the pyranol base santalanol, which we propose to call santalylium chloride and which upon treatment with sodium acetate regenerates santalin without the intermediate formation of santalanol (cf. Irvine and Robinson, *J.*, 1927, 2086). Contrary to the expected conversion of an anhydrobenzopyranol into the methyl ether of hydroxybenzopyranol (cf., *e.g.*, Pratt and Robinson, *J.*, 1923, 739; Armit and Robinson, *J.*, 1925, 1604) the methylation of santalin with an excess of methyl sulphate and aqueous-methanolic sodium hydroxide or by the methyl iodide–potassium carbonate method gave rise to *O*-tetramethylsantalin $C_{27}H_{11}O_2(OMe)_7$, which retains the properties of a quinonoid anhydrobenzopyranol base and gives rise to the expected salts; the melting point and analytical results of *O*-tetramethylsantalin are in close agreement with those recorded for *O*-dimethylsantalin by Cain, Simonsen, and Smith (*loc. cit.*), and the molecular-weight determinations in boiling benzene are in accord with

the empirical formula now proposed. Further, methylation of *O*-tetramethylsantalin with methyl sulphate and potassium carbonate in boiling benzene (cf. Armit and Robinson, *loc. cit.*) furnished the optically inactive, colourless *O*-pentamethylsantalanol which readily gave rise to *O*-pentamethylsantalylium picrate and perchlorate.

In extensive studies on the degradation of santalin and its methyl ethers it was found that ozonolysis (in a variety of solvents), oxidation with hydrogen peroxide in acetic acid, methanol, or methanolic sodium hydroxide, or oxidation with chromic acid gave intractable products. *O*-Pentamethylsantalanol was surprisingly resistant to hot alkalis but *O*-tetramethylsantalin on degradation with concentrated aqueous-methanolic potassium hydroxide furnished 2 : 4-dihydroxy-5-methoxybenzaldehyde (I) in very low yield together with a complex mixture from which there were isolated by careful chromatography two colourless resinous products, (*a*) with an intense green and (*b*) with a deep brown ferric reaction. From the fraction (*a*) a semicarbazone $C_{28}H_{16}O_3N_3(OMe)_7$ and a 2 : 4-dinitrophenylhydrazone $C_{33}H_{17}O_6N_4(OMe)_7$ were prepared, which appear to retain the original carbon skeleton and thus correspond to derivatives of a styryl ketone derived from *O*-tetramethylsantalin. The second fraction, (*b*), from the hydrolysate furnished a semicarbazone and a 2 : 4-dinitrophenylhydrazone, the analytical results of which could not be satisfactorily equated with an empirical formula.

Oxidation of *O*-tetramethylsantalin with potassium permanganate under a variety of conditions gave rise to a complex mixture from which ultimately there were isolated veratraldehyde, veratric acid, and 2 : 4-dimethoxybenzoic acid. Despite a careful search *p*-anisic acid (cf. Cain, Simonsen, and Smith, *loc. cit.*) could not be detected among the acidic degradation products and it may well be that the pigment described by these authors, whilst similar in some respects, is not identical with the compound now described.

From the results of the foregoing degradation experiments it may reasonably be assumed that the 2 : 4-dihydroxy-5-methoxybenzaldehyde residue (I) is derived from an anhydrobenzopyrylium system in *O*-tetramethylsantalin where the hydroxyl group in the 2-position of the aldehyde arises from the oxonium ring and that in the 4-position is derived from the hemiquinone system, *i.e.*, the aldehyde (I) is derived from the residue (II) which cannot have a substituent in the 4-position. Further, if it is assumed that the veratraldehyde and veratric acid are derived from the same part of the molecule, the isolation of (I) along with the veratrole unit, together with the 2 : 4-dimethoxybenzoic acid, account for five of the seven methoxyl groups in *O*-tetramethylsantalin and, in conjunction with the unit (II), for seven of the nine oxygen atoms. Thus the remaining two oxygen atoms are present as methoxyl groups and, in agreement with the empirical formula

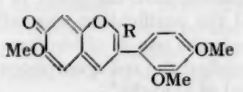


imply the presence of a fourth benzenoid system. Moreover, it is also reasonable to assume that the veratraldehyde residue, formed during the oxidation of *O*-tetramethylsantalin, probably arises from the oxidation of the enolic form of a deoxybenzoin system resulting

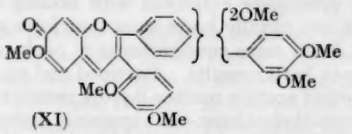
from the destruction of ring (A) of the residue (II), *i.e.*, the oxidative degradation proceeds by way of (III), (IV), (V). That the initial seat of oxidation in *O*-tetramethylsantalin is in ring (A) of (II) finds support in the extreme resistance of *O*-pentamethylsantalanol to hydrolysis or oxidation under comparable conditions. The oxidation route proposed to account for the production of veratraldehyde is supported by the results obtained in the oxidation of deoxybenzoins which can be best explained on the assumption that it is the enolic form which reacts with potassium permanganate (Part IV, *J.*, 1950, 2961; cf. Part V, *J.*, 1954, 1440). Therefore, if these views are correct the veratraldehyde and the veratric acid arise from a veratrole residue in the 3-position of the system (II) in *O*-tetramethylsantalin which may therefore be expanded to formula (VI). Since the *O*-dimethylresorcinol nucleus appears only as 2 : 4-dimethoxybenzoic acid, therefore to accommodate the dimethoxybenzene unit which apparently is destroyed in the oxidation, the residue R in (VI) may be expanded to a diphenyl system where the resorcinol unit is terminal as in (VII). Thus the quinonoid anhydropyranol base, *O*-tetramethylsantalin and the pyranol, *O*-pentamethylsantalanol, may be provisionally represented by the structures (VII) and (VIII) respectively where the position of the two methoxyl groups in ring (B) of the diphenyl system remains to be determined.

In agreement with numerous analytical results of the compound and its derivatives santarubin is best represented by the empirical formula $C_{27}H_{14}O_5(OMe)_4$. This quinonoid anhydro-base, which is devoid of *C*-methyl groups, closely resembles santalin, forming a well-defined hydrochloride, santarubylium chloride, and, on methylation by the methyl iodide–potassium carbonate method, an *O*-trimethyl ether, isomeric with *O*-tetramethylsantalin. Like this compound, *O*-trimethylsantarubin is a quinonoid anhydro-base, forming a well-crystallised picrate and giving by the methyl sulphate–benzene–potassium carbonate method, a benzopyranol, *O*-tetramethylsantarubanol, characterised by the formation of a picrate and perchlorate.

In its behaviour towards hydrolytic and oxidising agents *O*-trimethylsantarubin is practically identical with *O*-tetramethylsantalin. With hot concentrated alkali it gave 2 : 4-dihydroxy-5-methoxybenzaldehyde (I), implying the presence of the residue (II) in the molecule. In addition a complex resinous product was formed from which there was prepared a 2 : 4-dinitrophenylhydrazone $C_{33}H_{17}O_8N_4(OMe)_7$, isomeric with the corresponding product from *O*-tetramethylsantalin. On oxidation with potassium permanganate *O*-trimethylsantarubin furnished 2 : 4-dimethoxybenzaldehyde, 2 : 4-dimethoxybenzoic acid, and an acid, in all probability veratric acid. Consequently,



(X)



(XI)

since *O*-tetramethylsantalin and *O*-trimethylsantarubin are isomeric and have the common unit (I) present in a residue of type (II), by the same chain of reasoning *O*-trimethylsantarubin contains the unit (X) which can be expanded to type (XI) as representing the structure of this compound. The production of 2 : 4-dimethoxybenzaldehyde from *O*-trimethylsantarubin in place of veratraldehyde, as in the case of *O*-tetramethylsantalin, indicates the presence of the *O*-dimethylresorcinol residue in the 3-position of *O*-trimethylsantarubin.

Thus santalin and santarubin are regarded as partially methylated derivatives of two isomeric, similarly constituted, quinonoid heptahydroxyanhydro-bases with tetrahydroxydiphenyl substituents in the 2-position, the orientations of which are unknown. In agreement with this it was found that the ultra-violet absorption curves of santalin and santarubin are typical of quinonoid anhydro-benzopyranols. Although for the present the structures assigned to these compounds are regarded as provisional we believe that they contain the main essential features of the molecules and it is of interest that these formulæ are in a general way related to the structures of other constituents isolated from these

woods, *viz.*, pterocarpin and homopterocarpin (Part I, *J.*, 1940, 787), and santal (Part III, *J.*, 1949, 1571).

In view of the exceptional difficulties encountered in the isolation of large amounts of the pigments and in the degradation studies, experiments on the preparation of type compounds have been initiated with a view to the ultimate synthesis of the methyl ethers of santalin and santarubin.

Experimental

Extraction of Santalin.—After having been twice digested with boiling carbon tetrachloride, powdered commercial red sandalwood (Part I, *loc. cit.*) (6 kg.) was exhaustively extracted with ether in a Soxhlet apparatus, and the very viscous resin (*ca.* 360 g.), which separated in the Soxhlet boiler, was dissolved in ethyl acetate (1 l.). On being kept this solution gradually deposited a red crystalline solid which was repeatedly recrystallised from alcohol, giving *santalin* in salmon-pink needles (20—30 g.), m. p. 305° (decomp.) with previous darkening from *ca.* 290°, $\lambda_{max.}$ 506, 355, 316 mμ ($E^{1\%}_{1\,cm.}$ 430, 129, 272) [Found in specimen dried in a vacuum at 200° for 16 hr.: C, 67·5; H, 4·7; OMe, 16·4. $C_{27}H_{15}O_6(OMe)_3$ requires C, 68·2; H, 4·6; OMe, 17·0%]. The pigment, which is sparingly soluble in the usual organic solvents, has an intense violet ferric reaction in alcohol, and is readily soluble in 2N-aqueous sodium hydroxide from which it is precipitated unchanged by carbon dioxide.

Addition of concentrated hydrochloric acid (3 ml.) to a suspension of santalin (1 g.) in alcohol (10 ml.) initially furnished a clear solution which then slowly deposited santalylium chloride in deep red prisms, with a green reflex. Recrystallised from aqueous-alcoholic hydrochloric acid, this salt separated as a *dihydrate* in deep red prisms, m. p. 294° (decomp.) [Found: C, 59·6, 60·2, 60·0; H, 4·7, 4·9, 5·4; Cl, 6·2; OMe, 17·0, 13·3, 13·0. $C_{27}H_{16}O_6Cl(OMe)_3,2H_2O$ requires C, 60·0; H, 4·8; Cl, 5·8; OMe, 15·5%]. Addition of much water or aqueous sodium acetate to an alcoholic solution of this chloride furnished the parent anhydro-base.

When saturated aqueous-alcoholic (1 : 1) picric acid (5 ml.) was added to a suspension of santalin (0·5 g.) in alcohol (2 ml.), the clear solution initially formed slowly deposited *santalylium picrate* in rosettes of dark crimson, rhombic prisms, m. p. 208—211° (decomp.) after purification from aqueous alcohol containing 2% of picric acid [Found: C, 56·6, 57·1, 56·6; H, 4·1, 4·4, 4·1; N, 5·8; OMe, 11·0, 10·8. $C_{33}H_{18}O_{13}N_3(OMe)_3$ requires C, 57·0; H, 3·6; N, 5·6; OMe, 12·3%].

On saturation with hydrogen chloride the ethyl acetate mother-liquors remaining from the purification of santalin furnished a red amorphous precipitate (460 g.) which rapidly darkened in contact with air whilst moist with solvent. After drying rapidly in a desiccator the product was a friable red powder, stable to air; it is reserved for further investigation.

Santalin was also isolated by a similar process from commercial camwood or barwood, which had been previously extracted with boiling carbon tetrachloride, but the yield of the pure compound was usually lower than that from sandalwood and the purification was rather more difficult. With some consignments of camwood and barwood, the use of chloroform in place of ether gave better results. Barwood and camwood also furnished the red amorphous pigment from the ethyl acetate mother-liquors remaining after removal of santalin.

O-Tetramethylsantalin.—A vigorously agitated solution of santalin (1 g.) in a mixture of 20% aqueous sodium hydroxide (10 ml.) and methanol (25 ml.) was treated with methyl sulphate (50 ml.) and 20% aqueous sodium hydroxide (100 ml.) alternately, with the addition of more methanol as required to maintain a homogeneous mixture; if the reaction tended to become too violent the mixture was occasionally cooled. The colour ultimately changed from intense red to pale orange and simultaneously a red, alkali-insoluble solid separated. After the addition of water (100 ml.) to complete the separation of the product, this was collected, washed, and dissolved in methanol, and the solution was poured into an excess of saturated aqueous sodium acetate (agitate). The well-washed and dried precipitate (1 g.) was crystallised from methanol or from benzene–light petroleum (b. p. 60—80°) containing 1% of methanol, giving *O*-tetramethylsantalin as a *hydrate* in slender, pale orange needles (0·7 g.), m. p. 154—155° (decomp.), which had a negative ferric reaction in alcohol and were insoluble in 2N-aqueous sodium hydroxide [Found: C, 67·9, 67·3; H, 5·6, 5·9; OMe, 36·5, 36·7%; *M*, 569, 596, 585. $C_{27}H_{11}O_2(OMe)_7,H_2O$ requires C, 67·7; H, 5·8; OMe, 36·1%; *M*, 602. Calc. for $C_{27}H_{11}O_2(OMe)_7$: C, 69·9; H, 5·5; OMe, 37·2%; *M*, 584]. The molecular-weight estimations were performed in benzene solution by the Menzies–Wright elevation of b. p. method.

The same tetramethyl ether (1·5—1·7 g.) was obtained by methylating santalin (2 g.) with methyl iodide (15 ml.) and potassium carbonate (10 g.) in boiling acetone (100 ml.) for 6 hr.

O-Tetramethylsantalylium chloride separated from aqueous-alcoholic hydrochloric acid as a *hemihydrate* in bright red prisms, with a magnificent green reflex, m. p. 210° (decomp.) [Found: C, 64·9, 64·3, 64·4; H, 6·1, 5·6, 5·9; Cl, 5·1; OMe, 33·1. $C_{27}H_{12}O_2Cl(OMe)_7,0{\cdot}5H_2O$ requires C, 64·9; H, 5·5; C, 5·5; OMe, 34·5%].

O-*Tetramethylsantalylium picrate* crystallised from 2% alcoholic picric acid in clusters of slender, red needles, m. p. 130—131°, or in rosettes of rectangular, red plates, m. p. 180—183° (decomp.) [Found: C, 58·8; H, 4·5; N, 4·9, 4·6; OMe, 26·8, 27·3. $C_{33}H_{14}O_9N_3(OMe)_7$ requires C, 59·0; H, 4·3; N, 5·0; OMe, 26·7%]. On being heated, the specimen of lower m. p. resolidified at *ca.* 140° and then melted at 180—183° (decomp.).

O-*Tetramethylsantalylium perchlorate* separated from aqueous acetic acid–perchloric acid (5 : 1) in deep red, flat parellelograms, m. p. 214—216° (decomp.), or in crimson, long slender needles, m. p. 180—185° (decomp.) [Found: C, 59·0, 59·2, 59·3; H, 5·4, 5·2, 5·5; Cl, 5·3; OMe, 30·8, 30·5. $C_{27}H_{12}O_9Cl(OMe)_7$ requires C, 59·6; H, 4·8; Cl, 5·2; OMe, 31·7%]. This salt was very sparingly soluble in methanol and ethanol.

O-*Pentamethylsantalanol.*—On being heated under reflux for 6 hr. a solution of *O*-tetramethylsantalin (1 g.) in benzene (50 ml.), containing methyl sulphate (2 ml.) and potassium carbonate (10 g.), became almost colourless and on isolation the product was dissolved in methanol (15 ml.). From the solution (stirred), *O*-pentamethylsantalanol was precipitated by an excess of 2N-aqueous sodium hydroxide as a colourless solid (1 g.) which did not crystallise. The *picrate*, which was moderately soluble in methanol, separated from 2% methanolic picric acid in crimson needles, m. p. 184—185° (decomp.) with previous darkening from *ca.* 150° [Found: C, 60·3; H, 4·5; N, 5·0, 4·9; OMe, 30·0. $C_{33}H_{13}O_8N_3(OMe)_8$ requires C, 59·5; H, 4·5; N, 5·1; OMe, 30·0%]. The *perchlorate* separated from a large volume of methanol containing 2% of perchloric acid in deep red, diamond shaped plates with a magnificent green sheen, m. p. 245—246° (decomp.), sparingly soluble in methanol and moderately soluble in acetic acid [Found: C, 60·0; H, 5·1; Cl, 5·8; OMe, 35·0, 35·1. $C_{27}H_{11}O_8Cl(OMe)_8$ requires C, 60·1; H, 5·0; Cl, 5·0; OMe, 35·5%].

Degradation of O-*Tetramethylsantalin with Alkali.*—A solution of *O*-tetramethylsantalin (1 g.) and potassium hydroxide (15 g.) in water (10 ml.) and methanol (25 ml.) was refluxed for 3½ hr. in an atmosphere of nitrogen. The cooled combined hydrolysates from 6 experiments were diluted with water, and the brown precipitate (4 g.) collected. Extraction of the alkaline liquors with ether furnished only a trace of product. After acidification with 2N-sulphuric acid the aqueous liquors were exhaustively extracted with ether, and the brown resin thus obtained was purified by repeated sublimation at 120°/0·001 mm., giving 2 : 4-dihydroxy-5-methoxybenzaldehyde (10 mg.) in pale yellow needles, m. p. 149°, which had an intense green ferric reaction in alcohol and were identical with an authentic specimen (Found: C, 57·5; H, 5·1; OMe, 16·6%; *M*, 166. Calc. for $C_7H_5O_3{\cdot}OMe$: C, 57·1; H, 4·8; OMe, 18·4%; *M*, 168) (Head and Robertson, *J.*, 1931, 1241).

Chromatography of the brown alkali-insoluble product (3 g.) from benzene solution on aluminium oxide and elution with the same solvent furnished (*a*) an almost colourless, non-crystalline solid (0·4 g.) with an intense green-brown ferric reaction in alcohol, and (*b*) a pale yellow, non-crystalline solid (0·5 g.) with a deep brown ferric reaction in alcohol. A quantity (0·5 g.) of unchanged *O*-trimethylsantalin was obtained subsequently by washing the column with methanol.

Fraction (*a*) gave a *semicarbazone* forming prisms, m. p. 202° (decomp.), from benzene [Found: C, 63·1; H, 5·8; N, 7·1; OMe, 35·0. $C_{28}H_{16}O_3N_3(OMe)_7$ requires C, 63·7; H, 5·6; N, 6·4; OMe, 33·0%], and a 2 : 4-*dinitrophenylhydrazone* which separated from much alcohol in red needles or from ethyl acetate in short, stout, squat, deep crimson prisms, m. p. 233° (decomp.) with darkening at *ca.* 200° [Found: C, 61·2, 61·0; H, 5·3, 5·2; N, 6·9, 6·8; OMe, 29·9. $C_{33}H_{17}O_6N_4(OMe)_7$ requires C, 61·4; H, 4·9; N, 7·2; OMe, 27·8%]. By the standard method the semicarbazone was converted into the 2 : 4-dinitrophenylhydrazone, m. p. 233° (decomp.).

Fraction (*b*) gave a *semicarbazone* which separated from alcohol in orange-yellow prisms, m. p. 203° (decomp.) (Found: C, 62·3; H, 5·6; N, 7·1, 7·1; OMe, 36·0, 36·1%). This could not be converted into the 2 : 4-*dinitrophenylhydrazone* which, however, was prepared directly from the crude fraction (*b*) and formed crimson plates, m. p. 202° (decomp.), from ethyl acetate (Found: C, 59·8; H, 4·8; N, 7·6, 7·7; OMe, 30·2, 30·3%). A mixture of the 2 : 4-dinitrophenylhydrazones from fractions (*a*) and (*b*) had m. p. *ca.* 180°.

Oxidation of O-*Tetramethylsantalin.*—A solution of potassium permanganate (3 g.) in water (80 ml.) was added gradually during 5 hr. to *O*-tetramethylsantalin (1 g.), dissolved in acetone

(80 ml.). Next day the reaction mixtures from 3 experiments were combined, clarified with sulphur dioxide, and acidified with 2N-sulphuric acid (10 ml.). After the evaporation of the greater part of the acetone in a vacuum the residual mixture was saturated with ammonium sulphate and exhaustively extracted with ether. The combined ethereal extracts (*A*) were washed with 2N-aqueous sodium hydrogen carbonate (50 ml. × 3), and the acidified washings saturated with ammonium sulphate and exhaustively extracted with ether to give extract (*B*). Distillation of extract (*A*) furnished veratraldehyde as a colourless oil (*ca.* 100 mg.) which rapidly solidified and then had m. p. 45—46°, identified by comparison with an authentic specimen [Found: C, 65·5; H, 6·2; OMe, 38·0. Calc. for $C_7H_4O(OMe)_2$: C, 65·1; H, 6·0; OMe, 37·4%]. The 2 : 4-dinitrophenylhydrazone of this aldehyde had m. p. 262—263° (decomp.) and was identical (crystal form and solubilities) with an authentic specimen (Found: N, 16·2. Calc. for $C_{15}H_{14}O_6N_4$: N, 16·2%).

By a combination of distillation at 0·001 mm. and fractional crystallisation from benzene, the colourless solid (450 mg.) left on evaporation of extract (*B*) was separated into 2 : 4-dimethoxybenzoic acid, m. p. and mixed m. p. 105° [Found: C, 59·8; H, 5·7; OMe, 33·0. Calc. for $C_7H_4O_2(OMe)_2$: C, 59·4; H, 5·5; OMe, 34·1%], and veratric acid, m. p. and mixed m. p. 177° (Found: C, 60·0; H, 5·7; OMe, 33·6%).

Isolation of Santarubin.—The amorphous red solid (1·5 g.), which separated from the concentrated carbon tetrachloride extracts of camwood (or barwood) (300 g.) (Part I, *loc. cit.*), was repeatedly crystallised from alcohol, giving santarubin (0·2 g.) in chocolate-coloured prisms with an intense green reflex, m. p. *ca.* 325° (decomp.), $\lambda_{max.}$ 506, 353, 316 mμ ($E^{1\%}_{1\,cm.}$ 450, 144, 294) [Found, in specimen dried at 100°/0·01 mm. for 16 hr.: C, 68·7, 68·4; H, 5·0, 5·3; OMe, 24·5. $C_{27}H_{14}O_5(OMe)_4$ requires C, 68·6; H, 4·8; OMe, 22·9%]. This pigment, which is readily soluble in 2N-aqueous sodium hydroxide, forming a deep red-violet solution, is sparingly soluble in the usual organic solvents and has an intense red-violet ferric reaction in alcohol.

Santarubylium chloride separated from alcoholic hydrochloric acid as a *hydrate* in silky deep-red needles, which, on prolonged contact with the solvent changed to long, deep red, parallelograms, with a green-black reflex, m. p. 211—214° (decomp.) (for either crystalline form) [Found: C, 62·5, 62·5; H, 5·2, 5·2; Cl, 5·6, 5·1; OMe, 21·2. $C_{27}H_{15}O_5Cl(OMe)_4,H_2O$ requires C, 62·4; H, 4·9; Cl, 5·8; OMe, 20·9%]. The ferrichloride, picrate, and perchlorate could not be obtained crystalline.

O-*Trimethylsantarubin.*—Methylation of santarubin (2 g.) derived from camwood or barwood, by the methyl iodide–potassium carbonate method in boiling acetone during 8 hr. gave O-*trimethylsantarubin* which separated from methanol in orange needles (1·5 g.), m. p. 167—168° (decomp.) [Found, in specimen dried at 100°/0·01 mm. for 12 hr.: C, 69·2, 70·1; H, 5·4, 5·8; OMe, 36·2%; *M*, 618, 629. $C_{27}H_{11}O_2(OMe)_7$ requires C, 69·9; H, 5·5; OMe, 37·2%; *M*, 584]. This compound is insoluble in 2N-aqueous sodium hydroxide and has a negative ferric reaction in alcohol.

O-*Trimethylsantarubylium picrate* separated from 2% alcoholic picric acid in clusters of bright red, flat prisms, or red slender needles, m. p. 219° (decomp.) with darkening from *ca.* 200° [Found: C, 59·6, 59·5, 59·5; H, 4·6, 4·7, 4·6; N, 4·8, 4·5; OMe, 27·2, 27·5. $C_{33}H_{14}O_9N_3(OMe)_7$ requires C, 59·1; H, 4·3; N, 5·2; OMe, 26·7%].

The chloride, perchlorate, and ferrichloride could not be satisfactorily purified.

O-*Tetramethylsantarubanol.*—Methylation of *O*-trimethylsantarubin (1 g.) with methyl sulphate (2 g.) and potassium carbonate (10 g.) in boiling benzene (50 ml.) during 6 hr. furnished a quantitative yield of *O*-tetramethylsantarubanol as a colourless, amorphous solid which could not be crystallised. The readily formed *perchlorate* separated from methanol, containing 2% perchloric acid, in long, slender, crimson prisms, m. p. 178—180° (decomp.), which on prolonged contact with the solvent changed to almost black tablets, m. p. 178—180° (decomp.) [Found: C, 60·4, 60·4; H, 4·9, 5·1; Cl, 4·9, 5·1, 5·1; OMe, 36·1, 33·6. $C_{27}H_{11}O_5Cl(OMe)_8$ requires C, 60·1; H, 5·0; Cl, 5·1; OMe, 35·5%]. The *picrate* separated from a large volume of alcohol in long slender, crimson needles, m. p. 215—217° (decomp.) [Found: C, 59·7, 59·5, 59·5, 59·6, 60·0; H, 4·2, 4·6, 4·7, 4·6, 4·5; N, 4·3, 4·3, 4·9, 4·6, 4·7; OMe, 30·2, 30·1, 30·3. $C_{33}H_{13}O_8N_3(OMe)_8$ requires C, 59·5; H, 4·5; N, 5·1; OMe, 30·0%].

The chloride and ferrichloride were amorphous.

Degradation of O-*Trimethylsantarubin with Alkali.*—Degradation of *O*-trimethylsantarubin (1 g.) from either camwood or barwood by the method used for *O*-tetramethylsantalin gave 2 : 4-dihydroxy-5-methoxybenzaldehyde in pale yellow needles, (5 mg.), m. p. and mixed m. p. 148°, together with a non-crystalline resin which furnished a 2 : 4-*dinitrophenylhydrazone* which separated from much alcohol or a small volume of ethyl acetate in slender, crimson needles,

m. p. 222° (decomp.) [Found: C, 60·9, 60·5; H, 5·1, 5·2; N, 7·3, 7·4; OMe, 29·5, 29·5. $C_{33}H_{17}O_6N_4(OMe)_7$ requires C, 61·4; H, 4·9; N, 7·2; OMe, 27·8%].

Oxidation of O-Tetramethylsantarubin.—Oxidation of *O*-trimethylsantarubin (1 g. × 3) was effected by the method used for *O*-tetramethylsantalin, and the product resolved into neutral and acidic fractions. From the neutral portion 2 : 4-dimethoxybenzaldehyde was obtained (15 mg.), m. p. and mixed m. p. 71—72°, giving a 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 257—258° (decomp.) (Found: N, 15·4. Calc. for $C_{15}H_{14}O_6N_4$: N, 16·2%). By distillation (at 0·001 mm.) and fractional crystallisation from benzene 2 : 4-dimethoxybenzoic acid (10 mg.), m. p. 108°, was isolated from the acidic fraction and was identified by comparison with an authentic specimen. The residue (10 mg.) left on the removal of this acid was purified by sublimation followed by crystallisation from benzene and then had m. p. *ca.* 150° (yield, *ca.* 3 mg.); admixed with veratric acid, it had m. p. *ca.* 170°.

UNIVERSITY OF LIVERPOOL. [*Received, March 27th,* 1954.]

Chemical Examination of Tylophora asthmatica. *Part I.*

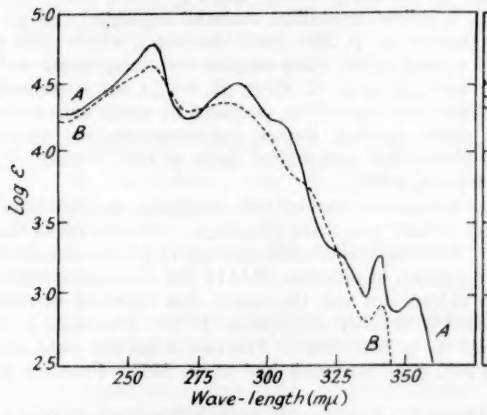
By T. R. GOVINDACHARI, B. R. PAI, and K. NAGARAJAN.

[Reprint Order No. 5192.]

Two alkaloids, tylophorine and tylophorinine, have been isolated from *Tylophora asthmatica* and separated by chromatography. Tylophorine has been degraded by three successive Hofmann exhaustive methylations to a nitrogen-free product $C_{24}H_{24}O_4$. The flavone isolated from *Tylophora asthmatica* is shown to be kæmpferol.

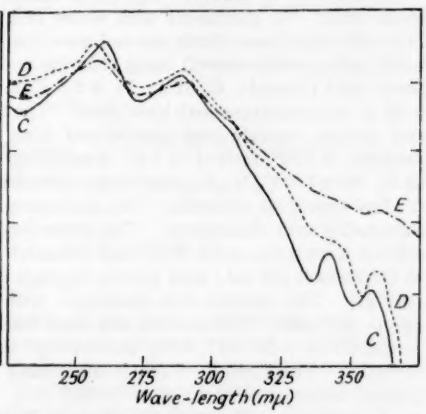
FROM *Tylophora asthmatica*, Wight et Arn., a perennial climber belonging to the natural order Asclepiadacæ, Ratnagiriswaran and Venkatachalam (*Indian J. Med. Res.*, 1935, **22**,

FIG. 1.



A, ———, Tylophorine. *B*, – – – –, Tylophorinine. (Both in ethanol.)

FIG. 2.



C, ———, Tylophorinemethine. *D*, – – – –, de-*N*-Methyltylophorinemethine. *E*, — · — · —, Nitrogen-free compound from tylophorine. (All in ethanol.)

433) isolated two alkaloids, tylophorine and tylophorinine, to which they assigned the molecular formulæ, $C_{24}H_{27}O_4N$ and $C_{23}H_{27}O_4N$ respectively. Tylophorine was shown to have four and tylophorinine three methoxyl groups. Chopra, Ghosh, Bose, and Ghosh (*Arch. Pharm.*, 1937, **275**, 236) could isolate tylophorine from *T. asthmatica* but not tylophorinine, although they obtained a second, amorphous base, m. p. 125—130°, which was not further characterised. In the present study, both tylophorine and tylophorinine were isolated, in conformity with the finding of Ratnagiriswaran and Venkatachalam.

A flavone, $C_{15}H_{10}O_6$, m. p. 268—269°, was also isolated and its identity with kæmpferol (Kostanecki, *Ber.*, 1901, **34**, 3723) was established.

Tylophorine and tylophorinine were separated by chromatography, without having recourse to the elaborate procedure of the earlier authors. Tylophorinine, when chromatographically purified, melts at 248—249° (decomp.), whereas the earlier authors report m. p. 232—233°. Further, tylophorinine nitrate has been reported to melt at 205—206°: the pure nitrate melts at 240—242°. The ultra-violet absorption spectra of tylophorine and tylophorinine are recorded in Fig. 1.

Tylophorine was found to contain no *N*-methyl group, but readily yielded a methiodide, $C_{24}H_{27}O_4N,CH_3I$, indicating the tertiary nature of the nitrogen atom. The methiodide was converted into a methohydroxide which at 100° *in vacuo* yielded tylophorinemethine, $C_{25}H_{29}O_4N$. A second Hofmann exhaustive methylation then yielded de-*N*-methyltylophorinemethine, $C_{26}H_{31}O_4N$, and a third application of this degradation gave a nitrogen-free product, $C_{24}H_{24}O_4$. The ultra-violet absorption spectra of these degradation products are recorded in Fig. 2. The evidence so far obtained indicates clearly that the nitrogen atom in tylophorine is common to two rings. The ready degradation to a nitrogen-free product by the Hofmann procedure also indicates the presence of three hydrogen atoms in β-positions with respect to the nitrogen atom. Further work is in progress.

Experimental

Extraction.—Powdered plant material (10 kg., whole plant) was extracted by percolation at room temperature with 90% alcohol containing 1% of acetic acid. The extract was concentrated to a syrup under reduced pressure. The dark brownish-green syrupy residue was extracted repeatedly with 0·5N-sulphuric acid until the acid extract no longer gave a precipitate with Mayer's reagent. The acid extract was concentrated to 1 l. *in vacuo*, filtered free from resin, and extracted repeatedly with ether. The ether and the aqueous layers were then separately worked up.

Isolation of the flavone. The ether extract, on removal of ether, yielded a residue containing acetic acid. On treatment with water (2 l.), a yellow crystalline material separated (1·2 g.). Crystallisation from dilute alcohol gave the flavone, m. p. 268—269° (decomp.), which gave a violet colour with neutral ferric chloride and a pink colour when treated with magnesium and acetic acid (Found: C, 62·4; H, 3·7. Calc. for $C_{15}H_{10}O_6$: C, 62·9; H, 3·5%), not depressed in m. p. on admixture with kæmpferol. The *tetra-acetyl* derivative, prepared by acetic anhydride and sodium acetate and crystallised from dilute alcohol, formed colourless needles, which softened at 120°, melted at 135°, resolidified above 135°, and melted again at 176° (Found: C, 58·8; H, 4·4. $C_{23}H_{18}O_{10},H_2O$ requires C, 58·5; H, 4·2%).

Isolation of the alkaloids. The acid extract was cooled, basified with ammonia, and extracted repeatedly with chloroform. The chloroform extract was dried (Na_2SO_4). On removal of the solvent a brownish solid (9 g.) was obtained. The crude alkaloidal mixture (1 g.) was dissolved in chloroform (30 ml.) and passed through a column of alumina (B.D.H. for chromatography) (100 g.). The column was developed with chloroform and the eluate was collected in nine 50-ml. portions. The column was then washed with ether–chloroform (1 : 1). Fractions 1—4 (respectively 0·28, 0·17, 0·09, and 0·05 g.) had m. p. 285—286°. Fraction 5 did not yield any material. Fractions 6—9 (each containing 0·01 g. of material) had m. p. 245°. Fraction 10 yielded material (0·02 g.) of m. p. 242°.

Tylophorine. Material obtained in fractions 1—4 separated from chloroform–alcohol as colourless crystals, m. p. 286—287° (decomp.), $[\alpha]_D^{27}$ −11·6° (*c*, 1·07 in $CHCl_3$), $\lambda_{max.}$ 255, 290, 340, 352 mμ (log ε 4·74, 4·49, 3·30, 2·93) (Found: C, 73·0; H, 6·5; N, 4·0. Calc. for $C_{24}H_{27}O_4N$: C, 73·2; H, 6·9; N, 3·6%). The *nitrate*, prepared by digestion with hot 5% nitric acid in alcohol and recrystallised from water, melted at 265—267° (Found: C, 62·7; H, 6·1; N, 6·2. $C_{24}H_{28}O_7N_2$ requires C, 63·1; H, 6·2; N, 6·1%). The *methiodide*, prepared in quantitative yield by refluxing the base with excess of methyl iodide in chloroform solution for 1 hr. and crystallised from water, had m. p. 280° (Found: C, 55·6; H, 5·8; N, 2·5; I, 23·4. $C_{25}H_{30}O_4NI$ requires C, 56·0; H, 5·6; N, 2·6; I, 23·7%).

Tylophorinine. Material obtained from fractions 6—10 and crystallised from chloroform–alcohol had m. p. 248—249°, $[\alpha]_D^{27}$ −14·2° (*c*, 1·76 in $CHCl_3$), $\lambda_{max.}$ 258, 287, 340 mμ (log ε 4·61, 4·34, 2·91) (Found: C, 72·0; H, 6·8. Calc. for $C_{23}H_{27}O_4N$: C, 72·4; H, 7·1%). The *nitrate*

after crystallisation from water melted at 240—242° (Found: C, 61·8; H, 6·8. $C_{23}H_{28}O_7N_2$ requires C, 62·1; H, 6·3%).

Hofmann Degradation of Tylophorine.—(a) *Tylophorinemethine.* A suspension of tylophorine methiodide (2·5 g.) in water (300 ml.) was shaken with silver oxide (from 10 g. of silver nitrate) for 4 hr. The mixture was filtered and the filtrate evaporated at 45—50° *in vacuo* to dryness. The residue was heated at 100°/0·5 mm. for 30 min., and then extracted repeatedly with hot benzene. The filtered benzene extract after removal of solvent yielded the *methine* (1·45 g.), m. p. 185—186°. Recrystallisation from benzene yielded colourless needles, m. p. 190°, $\lambda_{max.}$ 261, 288, 343, 358 mμ (log ε 4·80, 4·53, 3·30, 3·10) (Found: C, 73·2; H, 7·3; N, 3·4. $C_{25}H_{29}O_4N$ requires C, 73·7; H, 7·1; N, 3·4%).

The *methiodide* was obtained by refluxing the methine (1·3 g.) in chloroform (5 ml.) with methyl iodide (5 ml.) for 4 hr. The precipitate (1·6 g.) was filtered off, washed with chloroform, and crystallised from methanol. It melted at 190° and decomposed above 250° (Found: C, 56·3; H, 6·0; N, 2·5; I, 23·6. $C_{26}H_{32}O_4NI$ requires C, 56·8; H, 5·8; N, 2·6; I, 23·1%).

(b) *de*-N-*Methyltylophorinemethine.* The methine methiodide (1·6 g.) was shaken in warm water (250 ml.) with silver oxide (from 10 g. of silver nitrate) for 5 hr. Further operations were conducted as previously. *De*-N-*methyltylophorinemethine* (1·02 g.), crystallised from 80% alcohol, sintered at 158° and melted at 167°, $\lambda_{max.}$ 258, 290, 344, 360 mμ (log ε 4·78, 4·58, 3·38, 3·18) (Found: C, 74·4; H, 7·3; N, 3·1. $C_{26}H_{31}O_4N$ requires C, 74·1; H, 7·4; N, 3·3%).

The *methiodide* was obtained by methyl iodide in chloroform at room temperature for a few hours. Crystallised from methanol–ether it melted at 196° (Found: C, 57·1; H, 6·0. $C_{27}H_{34}O_4NI$ requires C, 57·6; H, 6·0%).

(c) *Nitrogen-free product.* The foregoing methiodide (0·8 g.), when submitted to the Hofmann degradation as previously, yielded a nitrogen-free *product* (0·5 g.). Repeated crystallisations from benzene–light petroleum mixture yielded pale yellow crystals, m. p. 152—153°, $\lambda_{max.}$ 260, 290, 360 mμ (log ε 4·65, 4·50, 3·60) (Found: C, 75·9; H, 6·1. $C_{24}H_{24}O_4$ requires C, 76·6; H, 6·4%).

We are grateful to Professor T. R. Seshadri for the gift of an authentic specimen of kæmpferol and to Mr. S. Selvavinayakam for microanalyses. We thank the Government of India for the award of a scholarship to one of us (K. N.) and Mr. R. Peter for assistance in the extraction of plant material.

PRESIDENCY COLLEGE, MADRAS. [*Received, March 9th,* 1954.]

Coenzyme A. Part IX. The Synthesis of Pantothenoylcysteine, its 4′-Phosphate, and Related Compounds as Possible Precursors of the Coenzyme.*

By J. BADDILEY and A. P. MATHIAS.

[Reprint Order No. 5289.]

Several derivatives of pantothenic acid have been synthesised and examined as possible precursors of coenzyme A in micro-organisms. These include pantothenoylcysteine and its 4′-phosphate, dipantothenoylcystine and its 4′-phosphate, pantothenamide, pantothenamidoacetaldehyde, *N*-2-hydroxyethylpantothenamide, and peptides of pantothenic acid with glycine, α-alanine, β-alanine, serine, and glutamic acid.

Brown and Snell's observation (*J. Amer. Chem. Soc.*, 1953, **75**, 2782) that pantothenoylcysteine is a precursor of coenzyme A in *Acetobacter suboxydans* is confirmed. Some bacteria can utilise other peptides of pantothenic acid.

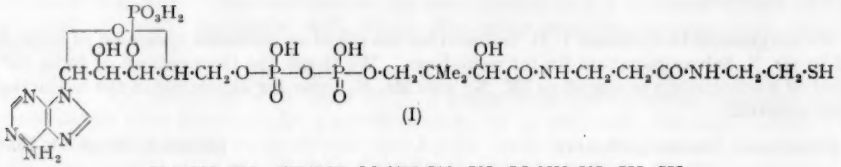
IT is now known (Levintow and Novelli, Abs. Amer. Chem. Soc. Meeting, Atlantic City, 1952, p. 33c; Baddiley, Thain, Novelli, and Lipmann, *Nature*, 1953, **171**, 76) that intermediate stages in the biological synthesis of coenzyme A (CoA) (I) involve pantetheine (II), pantetheine-4′-phosphate, and 3′-dephospho CoA. However, when this work was started little was known about the stages in the conversion of pantothenic acid into pantetheine (II)

* Part VIII, *J.*, 1953, 1610.

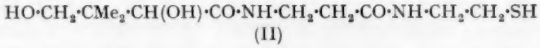
or its 4′-phosphate. This paper describes the synthesis of several derivatives of pantothenic acid which, for various reasons, were considered as possible CoA precursors.

Lactobacillus arabinosus can convert pantetheine into CoA. However, it does not produce CoA from pantothenic acid unless cystine is present in the medium (Pierpoint and Hughes, *Biochem. J.*, **1954**, **56**, 130). The fact that cystine cannot be replaced by 2-mercaptoethylamine implies that pantetheine is not formed by the condensation of pantothenic acid with 2-mercaptoethylamine, the latter arising from the decarboxylation of cysteine. Possible mechanisms for pantetheine synthesis include the formation of pantothenoylcysteine (III*a*) and subsequent decarboxylation, or the formation of a pantothenoyl-peptide followed by transfer of a thiol group from cysteine. In an effort to decide between these alternatives we have synthesised pantothenoylcysteine and several sulphur-free peptides of pantothenic acid, and their behaviour towards growth and CoA-production in micro-organisms has been examined.

Pantothenoylcysteine (III*a*) or the corrresponding disulphide was synthesised by four different routes. In the first route the mixed carbonic anhydride obtained from pantothenic acid and ethyl chloroformate (Wieland and Bokelmann, *Naturwiss.*, 1951, **38**, 384) was allowed to react with *S*-benzylcysteine to give impure *S*-benzylpantothenoylcysteine (V). The benzyl group was removed by reduction with sodium in liquid ammonia, yielding impure pantothenoylcysteine. A pure sample of pantothenoylcysteine, necessary for biological evaluation, was obtained by chromatography on a cellulose column in butanol–water. The pure substance contained no free amino-group, gave a strong thiol reaction with nitroprusside, and a slowly developing ninhydrin reaction typical of a peptide. All the pantothenic acid derivatives and peptides described in this paper gave very weak ninhydrin reactions but their presence could be demonstrated by the chlorine–



(I)



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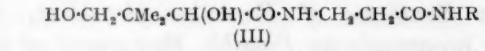

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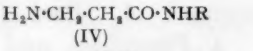
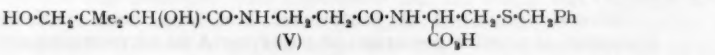


(IV)

(*a*) R = $-CH(CO_2H)\cdot CH_2\cdot SH$
(*b*) R = $-CH(CO_2H)\cdot CH_2\cdot OH$
(*c*) R = $-CH_2\cdot CH_2\cdot OH$
(*d*) R = $-CH_2\cdot CHO$
(*e*) R = $-CH_2\cdot CO_2H$
(*f*) R = $-CH_2\cdot CH_2\cdot CO_2H$
(*g*) R = $-CH(CO_2H)\cdot CH_3$
(*h*) R = H
(*i*) R = $-CH(CO_2H)\cdot CH_2\cdot CH_2\cdot CO_2H$



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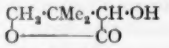

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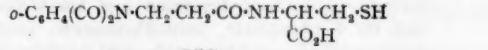

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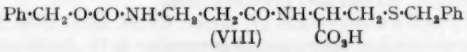

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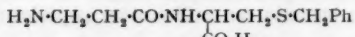

(IX)

starch–iodide method (Buchanan, personal communication; Rydon and Smith, *Nature*, 1952, **169**, 922).

Two other routes to pantothenoylcysteine involve the preparation of β-alanylcysteine (IV*a*) and its reaction with pantolactone (VI). The general peptide synthesis in which amino-groups are protected as their phthaloyl derivatives (Sheehan and Frank, *J. Amer.*

Chem. Soc., 1949, **71**, 1856; Kidd and King, *Nature*, 1948, **162**, 776) was successful but inconvenient. Although phthaloyl-β-alanine chloride and cysteine readily gave phthaloyl-β-alanylcysteine (VII), removal of the phthaloyl residue was difficult. β-Alanylcysteine and its disulphide were obtained more easily by the benzyloxycarbonyl peptide synthesis. Benzyloxycarbonyl-β-alanine chloride and *S*-benzylcysteine gave *S*-benzyl-*N*-(benzyloxycarbonyl-β-alanyl)cysteine (VIII). Both the benzyloxycarbonyl and the benzyl group were removed by reduction with sodium in liquid ammonia, and the purified product consisted of a mixture of β-alanylcysteine (IV*a*) and its disulphide. These were readily interconvertible by oxidation with iodine or reduction with sodium in liquid ammonia, and their constitutions were established by acid hydrolysis to β-alanine and cystine.

The most satisfactory synthesis of pantothenoylcysteine involved conversion of the *S*-benzyl derivative (VIII) into *S*-benzyl-β-alanylcysteine (IX) by reduction with sodium in liquid ammonia and re-benzylation of the thiol group *in situ*. The benzyl peptide was then condensed with pantolactone to give *S*-benzyl-*N*-(D-pantothenoyl)cysteine (V) from which the benzyl group was removed with sodium in liquid ammonia.

Pantothenoylserine (III*b*) was best prepared by treating benzyloxycarbonyl-β-alanine with ethyl chloroformate followed by serine, to give benzyloxycarbonyl-β-alanylserine. Removal of the benzyloxycarbonyl group by catalytic hydrogenolysis yielded β-alanylserine (IV*b*) which, when heated with pantolactone and dimethylamine in alcohol, gave pantothenoylserine in good yield (cf. B.P. 660,722). Pantothenoylserine containing considerable amounts of pantothenic acid was also prepared by the direct action of serine on the anhydride from pantothenic acid and ethyl chloroformate.

Benzyloxycarbonyl-β-alanine azide reacted readily with 2-hydroxyethylamine. The single neutral product did not evolve nitrogen when treated with nitrous acid and so contained no free amino-group. It was converted into *N*-β-alanyl-2-hydroxyethylamine (IV*c*) by hydrogenolysis with sodium in liquid ammonia. When this amide was heated with pantolactone, *N*-2-hydroxyethylpantothenamide (III*c*) was obtained in high yield. Pantothenoylglycine (III*e*), pantothenoyl-β-alanine (III*f*), pantothenoyl-α-alanine (III*g*), and pantothenoylglutamic acid (III*i*), were prepared by heating the respective β-alanyl-peptides (IV) with pantolactone and dimethylamine in alcohol and were purified through their readily crystallisable dimethylamine salts. Pantothenamide (III*h*) was obtained in good yield by heating β-alaninamide (IV*h*) with pantolactone, this being a more convenient method than that of Wieland, Molier, and Dieckelmann (*Chem. Ber.*, 1952, **85**, 1035).

The reaction of aminoacetaldehyde diethyl acetal with the mixed anhydride from pantothenic acid and ethyl chloroformate gave the pantothenoylamino-acetal. Cautious acid hydrolysis then liberated pantothenoyl aminoacetaldehyde (III*d*) which was characterised as its 2 : 4-dinitrophenylhydrazone and with silver oxide gave pantothenoylglycine.

While this work was in progress Brown and Snell (*J. Amer. Chem. Soc.*, 1953, **75**, 2782) and later King and Cheldelin (*Proc. Soc. Exp. Biol. N.Y.*, 1953, **84**, 591) announced that pantothenoylcysteine (synthesised independently by Bowman and Cavalla, unpublished work) is utilised by *A. suboxydans*, but not be *L. arabinosus*, as a CoA precursor. Pantothenoylcysteine, prepared by us, has been examined by Drs. D. E. Hughes and W. S. Pierpoint who confirm these findings.

Brown and Snell suggested that pantothenoylcysteine-4′ phosphate (X) might be a CoA precursor. We have synthesised it by a route essentially similar to the synthesis of

$$\underset{\text{(X)}}{H_2O_3PO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}\underset{CO_2H}{CH}{\cdot}CH_2{\cdot}SH}$$

pantetheine-4′ phosphate (Part VIII). *S*-Benzylpantothenoylcysteine (V) was phosphorylated with dibenzyl phosphorochloridate in pyridine, and benzyl groups were removed with sodium in liquid ammonia. Under these conditions the 2′-hydroxyl group is unaffected. The structure of the product was proved by hydrolysis to cysteine and pantothenic acid-4′ phosphate (Baddiley and Thain, *J.*, 1951, 246).

Pantothenoylcysteine-4′ phosphate had about 40% of the activity of pantothenyl cysteine and twice the activity of pantothenic acid in the growth of *A. suboxydans*. This may mean that dephosphorylation to pantothenoylcysteine occurs before conversion into

CoA. However, it is possible that different micro-organisms adopt different routes or sequences for the synthesis of the coenzyme. In support of this is the observation (Baddiley, Hughes, Mathias, and Pierpoint, *Biochem. J.*, 1954, **56**, xxii) that *L. arabinosus* can phosphorylate pantothenic acid itself to pantothenic acid-4′ phosphate. It is not yet known whether this represents a normal step in the conversion of pantothenic acid into CoA in this organism but, if so, it would seem that pantothenoylcysteine-4′ phosphate must also be an intermediate. The failure of this organism to respond to external supplies of the phosphorylated intermediates would be ascribed to their inability to penetrate the cells.

Of the other peptides described here only two were significantly active towards growth of, or CoA-production in, a variety of organisms tested. Pantothenoyl-β-alanine (III*f*) had 20—30% of the activity of pantothenic acid in supporting the growth of *Proteus morganii*. Pantothenoylglycine (III*e*) was variable in its effect on *L. arabinosus*: it had 30—80% of the activity of pantothenic acid when cystine was present in the medium. It seems likely that both these substances owe their effect to hydrolysis to pantothenic acid by peptidases in these organisms. The complete inactivity of all the other sulphur-free peptides described here suggests that rather specific β-alanine- and glycine-peptidases are present in the respective organisms.

Experimental

Phthaloyl-β-alanylcysteine.—A solution of phthaloyl-β-alanine chloride (2·37 g.) (Gabriel, *Ber.*, 1908, **41**, 243) in dioxan (50 c.c.) was added with stirring to sodium hydrogen carbonate (2·7 g.) in water (100 c.c.) containing L-cysteine hydrochloride (1·57 g.) at 0—5°. The mixture was kept for 1 hr. at room temperature, then acidified (Congo-red) with hydrochloric acid, and evaporated *in vacuo* to a small volume. The crystalline *peptide* was filtered off, washed with water, and dried. Recrystallised from alcohol it had m. p. 164—165° (2·7 g.) (Found: C, 52·0; H, 4·5; N, 8·8; S, 9·5. $C_{14}H_{14}O_5N_2S$ requires C, 52·0; H, 4·4; N, 8·7; S, 10·0%). When examined by paper chromatography in butanol–acetic acid–water it had R_F 0·82.

Di-β-alanylcystine (*Method* I).—Phthaloyl-β-alanylcysteine (1 g.) and 90% hydrazine hydrate (0·18 c.c.) in alcohol (10 c.c.) were refluxed for 3 hr. Solvent was removed under reduced pressure and the residue was triturated with N-hydrochloric acid (5 c.c.) for 20 min. Undissolved material was filtered off and washed with a little dilute hydrochloric acid, then with water. Combined filtrate and washings were passed through a column of Amberlite IRA-400 resin (formate form) to remove chloride ions. The effluent was concentrated under reduced pressure, then acetone and alcohol were added. The white precipitate (0·3 g., 50%) consisted of two components (R_F 0·11 and 0·29), the latter being present only in small amount. The minor component was removed by fractional precipitation from aqueous solution with alcohol and acetone. The more soluble *peptide* (R_F 0·11 in butanol–acetic acid–water) was thus obtained pure (Found: C, 37·0; H, 5·9; N, 14·6; S, 16·8. $C_{12}H_{22}O_6N_4S_2$ requires C, 37·7; H, 5·8; N, 14·7; S, 16·8%).

Hydrolysis. A sample (10 mg.) was heated with 6N-hydrochloric acid in a sealed tube at 100° for 3 hr. The hydrolysate was evaporated to dryness in a desiccator. A second sample was treated with hydrogen peroxide (0·1 c.c.; 30-vol.) at room temperature for 30 min., then gently warmed to decompose excess of peroxide. The solution was diluted with an equal volume of concentrated hydrochloric acid and hydrolysed as above. Examination of these two hydrolysates by paper chromatography in *n*-propanol–ammonia–water (6 : 3 : 1) showed that the first contained β-alanine (R_F 0·29) and cystine (R_F 0·17), and the second β-alanine and cysteic acid (R_F 0·23).

S-*Benzyl*-N-(*benzyloxycarbonyl*-β-*alanyl*)*cysteine.*—Benzyloxycarbonyl-β-alanine chloride (Sifferd and du Vigneaud, *J. Biol. Chem.*, 1935, **108**, 753) (prepared from benzyloxycarbonyl-β-alanine, 2·23 g.) in dry ether (15 c.c.) was added with shaking to a solution of *S*-benzyl-L-cysteine (2·11 g.) (Wood and du Vigneaud, *ibid.*, 1939, **130**, 110) in 2N-sodium hydroxide (10·5 c.c.) at 0°. The sodium salt of the product crystallised during the reaction. After 1 hr. at room temperature water was added to dissolve the precipitate. The ethereal layer was separated and discarded. The aqueous layer was acidified (Congo-red) with 5N-hydrochloric acid, and the precipitate filtered off, washed with water, then dried. The finely powdered material was thoroughly washed with ether to remove benzyloxycarbonyl-β-alanine, then extracted with boiling ethyl acetate (3 × 50 c.c.). The combined extracts were evaporated to dryness under reduced pressure, and the residue was recrystallised from ethyl acetate. The *benzyloxycarbonyl*

compound crystallised as prisms, m. p. 122—124° (3·4 g., 78%) (Found: C, 60·7; H, 5·4; N, 6·6; S, 8·0. $C_{21}H_{24}O_5N_2S$ requires C, 60·6; H, 5·8; N, 6·7; S, 7·7%).

β-Alanylcysteine and its Disulphide. (*Method* II.)—Small pieces of sodium were added to a solution of *S*-benzyl-*N*-(benzyloxycarbonyl-β-alanyl)cysteine (2·0 g.) in liquid ammonia (25 c.c.) until a persistent blue colour was produced. Excess of sodium was destroyed by adding glacial acetic acid in ammonia. Solvent was evaporated under reduced pressure and the residue treated with a suspension of Amberlite IRC-50 resin (ammonium form) in ice-water (50 c.c.). The turbid suspension was poured on to a column of IRC-50 (ammonium form) which was then washed with water. The effluent was washed with ether, concentrated under reduced pressure, and diluted with alcohol and ether, yielding white crystals (0·85 g., 92%). This mixture was resolved by a 55-stage counter-current distribution between the two phases of the butanol–acetic acid–water. Tubes 1 and 2 contained a slow-moving substance (R_F 0·11) and tubes 4—9 a faster-moving substance (R_F 0·29). Hydrolysis and paper chromatography as described above showed that both contained β-alanine and cysteine or cystine. The fractions were evaporated to small volume *in vacuo* and the peptides precipitated by addition of alcohol. *β-Alanylcysteine* (R_F 0·29) (0·5 g.) gave an intense colour with sodium nitroprusside after spraying with ammonia (Found: C, 37·4; H, 6·7; N, 14·2; S, 16·7. $C_6H_{12}O_3N_2S$ requires C, 37·5; H, 6·3; N, 14·6; S, 16·7%). Di-β-alanylcystine (R_F 0·11) (0·2 g.) was indistinguishable from the peptide obtained from phthaloyl-β-alanylcysteine. It gave no colour with nitroprusside but after reduction with potassium hydrogen sulphite–cyanide solution a positive thiol reaction was obtained (Found: C, 37·0; H, 6·0; N, 14·7%). β-Alanylcysteine was readily oxidised to this disulphide by iodine in aqueous sodium iodide.

NN′-*Di*-D-*pantothenoyl*-L-*cystine*.—β-Alanylcysteine (0·384 g.), D-pantolactone (0·26 g.), and dimethylamine (0·2 c.c.) were heated together in methanol (1·5 c.c.) for 8 hr. A small amount of undissolved solid was removed by centrifugation and washed with methanol. Combined supernatant liquid and washings were evaporated to dryness *in vacuo*. The crude product was dissolved in water, and the solution passed through a column of Amberlite IR-120 resin (H^+ form). The effluent was washed with ether, neutralised with dimethylamine, and evaporated to dryness, leaving a syrup (0·6 g., 82%). On paper it moved as a single spot (R_F 0·34), indistinguishable from that given by a sample of pantothenoylcysteine (prepared by the method described below) which had been oxidised with iodine in sodium iodide solution. Similarly, the above disulphide, after reduction with sodium in liquid ammonia, gives a spot (R_F 0·65) indistinguishable from that given by pantothenoylcysteine.

D-*Pantothenoyl*-L-*cysteine*.—Ethyl chloroformate (1·95 c.c.) was added dropwise with shaking to a solution of sodium pantothenate (4·82 g.) in dimethylformamide (30 c.c.) cooled to −5°. After 10 min., a solution of *S*-benzyl-L-cysteine (4·22 g.) in 1·025N-sodium hydroxide (19·5 c.c.) was added with vigorous stirring. The resulting solution was kept at room temperature for 1 hr. Solvents were evaporated under reduced pressure and the residue was dissolved in water. A small amount of *S*-benzylcysteine was filtered off, and the filtrate acidified (Congo-red) with dilute hydrochloric acid and extracted with chloroform (3 × 20 c.c.). The combined extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo* and the resulting syrup (7·7 g.) was dissolved in liquid ammonia. Metallic sodium was added in small pieces until a blue colour persisted for 30 min. The slight excess of sodium was destroyed with ammonium chloride, and ammonia was allowed to evaporate. The residue was dissolved in ice-water and the pH adjusted to 7 with sulphuric acid. A solution of mercuric sulphate (30%) in sulphuric acid (10%) was added with stirring until no further precipitation occurred. The precipitate was collected by centrifugation, washed with water, suspended in water, and decomposed by hydrogen sulphide. After filtration, the solution was neutralised with barium hydroxide and evaporated to dryness. Paper chromatography of the crude barium salt (8·7 g.) in butanol–acetic acid–water showed that the main component was a sulphur-containing peptide (R_F 0·65). A sulphur-containing peptide of R_F 0·85 and traces of unidentified substances were also present. An aqueous solution of the crude barium salt was passed through a column of Amberlite IR-120 resin (H^+ form), reprecipitated as the mercury salt, and isolated as its barium salt. This consisted of a mixture of the two sulphur-containing peptides only.

Purification by chromatography on cellulose. A column (110 × 2 cm.) of washed, powdered cellulose was equilibrated by thorough washing with butanol saturated with water. The crude barium salt (from above experiment) (250 mg.) was dissolved in water and barium removed by passage through a column of Amberlite IR-120 resin (H^+ form). Most of the solvent was removed *in vacuo* and the residue was dissolved in a little wet butanol. The solution was transferred to the column which was developed with saturated butanol. 100 fractions of

2 c.c. each were collected. Fractions 79—84 contained the substance of R_F 0·85, and fractions 87—100 the substance of R_F 0·65. The appropriate fractions were bulked and evaporated under reduced pressure. The residues were dissolved in water, neutralised with barium hydroxide, and evaporated to dryness. The barium salt of the substance, R_F 0·85 (90 mg.), was precipitated from aqueous alcohol with acetone–ether (Found : C, 27·9; H, 4·0; N, 4·2; S, 7·2; Ba, 23·8%). A sample of the free acid was hydrolysed for 1 hr. at 100° with concentrated hydrochloric acid. Paper chromatography of the hydrolysate in butanol–acetic acid–water and butanol–pyridine–water (65 : 35 : 65) indicated the presence of cysteine but absence of β-alanine. In the latter solvent mixture a second sulphur-containing, ninhydrin positive hydrolysis product (R_F 0·26) besides cysteine was observed. The barium salt of the substance of R_F 0·65 (110 mg.) was precipitated from alcohol by acetone and ether. This consisted of slightly impure *barium pantothenoylcysteine* salt (Found : C, 33·3; H, 5·0; N, 5·2; S, 5·3; Ba, 19·5. $C_{12}H_{21}O_6N_2SBa_{\frac{1}{2}}$ requires C, 36·9; H, 5·4; N, 7·2; S, 8·2; Ba, 17·6%). A sample of the free *acid* was prepared by removing barium ions with an Amberlite IR-120 column (H^+ form), then freeze-drying the eluate (Found : C, 45·3; H, 7·1; N, 7·7. $C_{12}H_{22}O_6N_2S$ requires C, 46·1; H, 6·8; N, 8·7%). Hydrolysis of the free acid and paper chromatography as described above indicated the presence of β-alanine and cysteine.

S-*Benzyl*-N-β-*alanyl*-L-*cysteine*.—Sodium (slight excess), in small pieces, was added to a solution of benzyloxycarbonyl-β-alanyl-*S*-benzyl-L-cysteine (41·6 g.) in liquid ammonia (500 c.c.), the excess being destroyed by ammonium chloride. Benzyl chloride (23 c.c.) was added dropwise with stirring. Ammonia was removed, finally at a water-pump. The residue was dissolved in ice-water (200 c.c.). The solution was washed with ether (2 × 50 c.c.) and adjusted to pH 6 by 5N-hydrochloric acid. The precipitate was filtered off and washed with water and alcohol. Recrystallisation from boiling water gave S-*benzyl*-N-β-*alanyl*-L-*cysteine* (23 g., 85%) as colourless needles, m. p. 233°, sharply depressed on admixture with *S*-benzylcysteine. In butanol–acetic acid–water it had R_F 0·65 (cf. *S*-benzylcysteine, R_F 0·65). It gave no colour with cyanide–nitroprusside, but was readily detected on paper by reaction with ninhydrin solution (yellow spot) or by the reagent of Winegard, Toennies, and Block (*Science*, **1948**, **108**, 506) (Found : C, 55·5; H, 6·0; N, 9·7; S, 11·5. $C_{13}H_{18}O_3N_2S$ requires C, 55·3; H, 6·4; N, 9·9; S, 11·3%).

S-*Benzyl*-N-D-*pantothenoyl*-L-*cysteine*.—D-Pantolactone (8·23 g.), β-alanyl-*S*-benzyl-L-cysteine (17·82 g.), and dimethylamine (6·2 c.c.) were heated together in dry boiling methanol (120 c.c.) for 21 hr. After cooling, the solution was filtered to remove unchanged β-alanyl-*S*-benzyl-L-cysteine (1·5 g.). The filtrate and washings were evaporated to dryness and the residue was dissolved in 20% ethanol. The solution was passed through a column of Amberlite IR-120 resin (H^+ form). The effluent was neutralised with barium hydroxide solution, and evaporated to dryness. Last traces of water were removed by repeated evaporation with dry ethanol. The residue was dissolved in dry ethanol (150 c.c.), and the barium salt precipitated by cautious addition, first of dry acetone, then dry ether. The *barium* salt was filtered off and washed quickly with dry acetone and ether, giving 25 g. (82%) of a white powder which travelled as a single spot (R_F 0·86) in butanol–acetic acid–water (Found : C, 46·0; H, 5·9; N, 5·9; S, 6·5; Ba, 14·5. $C_{19}H_{28}O_6N_2SBa_{\frac{1}{2}}$ requires C, 47·4; H, 5·8; N, 5·8; S, 6·7; Ba, 14·3%).

N-D-*Pantothenoyl*-L-*cysteine*.—Barium *S*-benzyl-*N*-D-pantothenoyl-L-cysteine (4·8 g.) was treated in liquid ammonia (*ca.* 50 c.c.) with sodium, the slight excess being destroyed by swirling the solution in air. Ammonia was removed and the powdery residue treated with a suspension of Amberlite IR-120 resin (H^+ form) in ice-water (this avoided the development of alkaline conditions on dissolution in water). The suspension was poured on to a column of IR-120 resin. The effluent was neutralised with barium hydroxide solution and evaporated to dryness under reduced pressure. The residue was dissolved in dry ethanol (50 c.c.) and *barium pantothenoylcysteine* precipitated by the cautious addition of dry acetone. It was separated by centrifugation, washed with acetone, and dried *in vacuo*, yielding an amorphous white powder (3·2 g., 82%) (Found : C, 36·2; H, 5·5; N, 7·1; S, 7·7. $C_{12}H_{21}O_6N_2SBa_{\frac{1}{2}}$ requires C, 36·9; H, 5·4; N, 7·2; S, 8·2%).

Paper chromatography in butanol–acetic acid–water showed that it was almost entirely in the thiol form (R_F 0·65), only a trace of the disulphide form (R_F 0·34) being present.

N-D-*Pantothenoyl*-L-*cysteine*-4′ *Dihydrogen Phosphate*.—Barium *S*-benzyl-*N*-D-pantothenoyl-L-cysteine (5 g.) was converted into the free acid by passage in aqueous ethanol (4 : 1) through Amberlite IR-120 (H^+ form). The eluate was evaporated to dryness under reduced pressure. The residue was evaporated twice with anhydrous benzene, and then dried (P_2O_5) at 10^{-3} mm. This material was dissolved in anhydrous pyridine (30 c.c.), the solution cooled to just above

the freezing point, and a solution of dibenzyl phosphorochloridate (prepared from dibenzyl phosphite, 4 g.; 1·5 mols.) in carbon tetrachloride was added dropwise with shaking. After 15 min. the flask was removed from the acetone–carbon dioxide bath and set aside at room temperature overnight. Pyridine was removed under reduced pressure, the residue dissolved in chloroform (50 c.c.), and the solution washed with 2N-sulphuric acid (2 × 20 c.c.) and water (2 × 20 c.c.). After being dried ($MgSO_4$), the chloroform was removed by evaporation, and the residue triturated with benzene. It was dissolved in liquid ammonia (*ca.* 50 c.c.) and treated with sodium, the excess being destroyed with ammonium acetate. Ammonia was allowed to evaporate. The powdery residue was added with stirring to a suspension of Amberlite IR-120 (H^+ form) in ice-water, and the suspension poured on to a short column of the same resin. The acid eluate was washed with ether and adjusted to pH 7 by barium hydroxide solution. The small amount of barium phosphate which separated was removed, and the solution evaporated to *ca.* 20 c.c. Ethanol (3 vols.) was added, and the precipitate centrifuged off, washed with ethanol, and dried *in vacuo*, yielding a white powder (2·5 g.). Paper chromatography in butanol–acetic acid–water and propanol–ammonia showed a major spot having the expected properties, a spot which appeared to be the disulphide form, and a number of contaminants, including a sulphur-free phosphate. Purification *via* the silver and copper salts was tried, but without success. The disulphide form was found to be less soluble in aqueous ethanol than the other components of the mixture. Repeated fractionation of the barium salt by precipitation from aqueous solution by ethanol gave a material which was practically homogeneous on paper chromatography (R_P 0·05 in both solvents). Alkaline hydrolysis (Part II, *J.*, 1951, 2253) gave pantothenic acid-4′ phosphate, and hydrolysis with 5N-hydrochloric acid after treatment with hydrogen peroxide gave β-alanine and cysteic acid. The impure fractions from the fractional precipitation were combined and dissolved in water, and the solution was adjusted to pH 8·5 with barium hydroxide solution and aerated with a brisk current of oxygen until the thiol test became negative. The solution was passed through a column of Amberlite IR-120 (H^+ form). The acid eluate was cautiously evaporated to dryness, and the residue submitted to 50-stage counter-current distribution between the two phases of butanol–acetic acid–water. At the end of the run, the tubes which gave a positive reaction with cyanide–nitroprusside (tubes 1—6) were evaporated separately to a small volume, diluted with aqueous ethanol, and again concentrated. This process was repeated until the smell of acetic acid was no longer noticeable. The residues were diluted with water to *ca.* 2 c.c. and neutralised with barium hydroxide solution. Addition of a large excess of ethanol precipitated the barium salts. From tube 1 was obtained an almost pure sample of the *barium* salt of the disulphide (Found : C, 22·4; H, 3·5; N, 4·2; S, 4·9; P, 4·7; Ba, 34·2. $C_{24}H_{38}O_{18}N_4S_2P_2Ba_3$ requires C, 23·8; H, 3·1; N, 4·6; S, 5·3; P, 5·1; Ba, 34·0%). The barium salts obtained from the other tubes were progressively more and more contaminated with impurities.

*Benzyloxycarbonyl-β-alanyl-*DL*-serine.*—Ethyl chloroformate (2·86 c.c.) was added slowly with shaking to a solution of benzyloxycarbonyl-β-alanine (6·7 g.) and triethylamine (4·22 c.c.) in dimethylformamide (30 c.c.) at −5°. The solution was kept for 15 min. at this temperature, then a solution of serine (3·15 g.) in 1·025N-sodium hydroxide (29·3 c.c.) was added rapidly with shaking. A vigorous evolution of carbon dioxide occurred. The solution, after 2 hr. at room temperature, was evaporated to dryness *in vacuo*. The residue was dissolved in warm water (100 c.c.), acidified (Congo-red) with hydrochloric acid, shaken with ether (3 × 100 c.c.) to remove benzyloxycarbonyl-β-alanine, and extracted with ethyl acetate (3 × 100 c.c.). The extract was dried ($MgSO_4$), then evaporated to dryness. *Benzyloxycarbonyl-β-alanyl-*DL*-serine* (4·5 g., 48%) had m. p. 127° after recrystallisation from ethyl acetate (Found : C, 54·6; H, 6·2; N, 8·9. $C_{14}H_{18}O_6N_2$ requires C, 54·2; H, 5·8; N, 9·0%). It had R_P 0·81 in butanol–acetic acid–water.

*β-Alanyl-*DL*-serine.*—A solution of benzyloxycarbonyl-β-alanylserine (1·2 g.) in methanol–acetic acid–water (44 : 3 : 3) (20 c.c.) was shaken with hydrogen in the presence of palladium oxide. After the uptake of hydrogen had ceased water was added to dissolve the precipitated product, and the catalyst was removed by filtration. The filtrate was evaporated to small bulk *in vacuo* and the peptide precipitated by alcohol. *β-Alanyl-*DL*-serine* crystallised as fine needles, m. p. 208—209° (decomp.) (0·65 g., 95%). It had R_F 0·32 in butanol–acetic acid–water (Found : C, 40·5; H, 6·8; N, 16·0. $C_6H_{12}O_4N_2$ requires C, 40·9; H, 6·8; N, 15·9%).

*Pantothenoyl-*DL*-serine.*—This was prepared from β-alanylserine (0·6 g.), pantolactone (0·443 g.), and dimethylamine (0·3 c.c.) (Found : C, 48·6; H, 8·5; N, 11·0. $C_{14}H_{29}O_7N_3$ requires C, 47·9; H, 8·3; N, 12·0%). The dimethylamine salt did not crystallise.

N-(*Benzyloxycarbonyl-β-alanyl*)-2-*hydroxyethylamine*.—A solution of benzyloxycarbonyl-β-alanine azide, prepared from the hydrazide (3·6 g.) (Sifferd and du Vigneaud, *loc. cit.*), in dry chloroform (20 c.c.), was added to a solution of 2-hydroxyethylamine (0·91 g.) in dry chloroform (5 c.c.). The resulting yellow solution was kept at room temperature overnight, then chloroform and hydrazoic acid were removed under reduced pressure. The *benzyloxycarbonyl* compound was recrystallised from ethyl acetate as fine needles, m. p. 123—124° (2·9 g., 72%) (Found: C, 58·6; H, 6·7; N, 10·2. $C_{13}H_{18}O_4N_2$ requires C, 58·6; H, 6·8; N, 10·5%).

N-β-*Alanyl*-2-*hydroxyethylamine*.—The preceding compound was treated in liquid ammonia with sodium, excess being destroyed with ammonium chloride and the ammonia allowed to evaporate. The residue was dissolved in ice-water and acidified (Congo-red) with hydrochloric acid. The solution was washed with ether, then evaporated to dryness *in vacuo*. The dry, powdered residue was extracted with boiling *iso*propyl alcohol (4 × 6 c.c.), and the combined extracts were evaporated to dryness *in vacuo*. The residual syrup was dissolved in water and acid removed by passing the solution through a column of Amberlite IR-4B resin (OH^- form). Solvent was removed and the resulting syrup sublimed ($110°/10^{-4}$ mm.), forming a very hygroscopic waxy solid, m. p. 49—50°. The β-alanyl compound had R_F 0·30 in butanol–acetic acid–water and formed a crystalline *hydrogen oxolate*, m. p. 115—116°, after recrystallisation from dilute oxalic acid solution (Found: C, 37·6; H, 6·3; N, 12·7. $C_7H_{14}O_6N_2$ requires C, 37·8; H, 6·3; N, 12·6%).

2-*Hydroxyethyl*-D-*pantothenamide*.—D(−)-Pantolactone (0·44 g.) and *N*-β-alanyl-2-hydroxyethylamine (0·45 g.) were heated together on a steam-bath for 2·5 hr. and the resinous product was washed by trituration with ether. Its solution in water was passed through a column of Amberlite IR-120 resin (H^+ form) to remove a little amino-compound, and the effluent evaporated to dryness *in vacuo*. 2-*Hydroxyethyl*-D-*p-antothenamide* was a colourless glass (0·8 g.) (Found: C, 49·8; H, 8·5; N, 10·6. $C_{11}H_{22}O_5N_2$ requires C, 50·4; H, 8·4; N, 11·1%). It had R_F 0·65 in butanol–acetic acid–water.

D-*Pantothenoylglycine*.—This synthesis started from D(−)-pantolactone (2·9 g.), β-alanylglycine (3·26 g.) (Hanson and Smith, *J. Biol. Chem.*, 1948, **175**, 833), and dimethylamine (2·3 c.c.), following a similar procedure to that described for the synthesis of pantothenoylcysteine. The free acid (5·5 g., 75%) was a syrup which readily formed a crystalline *dimethylamine* salt, prisms, m. p. 103—105° (from dry alcohol containing a little dimethylamine) (Found: C, 48·3; H, 8·6; N, 12·9. $C_{13}H_{27}O_6N_3$ requires C, 48·6; H, 8·4; N, 13·1%). On paper it had R_F 0·64 (butanol–acetic acid–water).

D-*Pantothenoyl*-β-*alanine*.—This was prepared from D(−)-pantolactone (1·3 g.), β-alanyl-β-alanine (1·6 g.) (Hanson and Smith, *loc. cit.*), and dimethylamine (1·0 c.c.) by a method similar to that described for the synthesis of pantothenoylglycine. The *dimethylamine* salt (2·7 g., 80%) formed needles, m. p. 122—124°, from alcoholic dimethylamine (Found: C, 49·8; H, 8·6; N, 12·2. $C_{14}H_{29}O_6N_3$ requires C, 50·2; H, 8·7; N, 12·5%).

N-(*Benzyloxycarbonyl*-β-*alanyl*)-L-*glutamic Acid*.—*iso*Butyl chloroformate (9·29 g.) was added slowly with shaking to a solution of benzyloxycarbonyl-β-alanine (15·7 g.) and triethylamine (9·55 c.c.) in dimethylformamide (75 c.c.) cooled to −5°. After 15 min. a solution of L-glutamic acid (10 g.) in 1·025N-sodium hydroxide (132·7 c.c.) was added rapidly. The solution was kept at room temperature for 2 hr. and then the solvents were removed *in vacuo*. The residue was dissolved in water (100 c.c.) and the solution acidified (Congo-red) with 5N-hydrochloric acid. After being washed with ether the solution was extracted with ethyl acetate (3 × 100 c.c.), and the combined extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. Unchanged benzyloxycarbonyl-β-alanine was removed by dissolution in ethyl acetate and addition of ether. The product was filtered off and dissolved in 40% ethanol, and the solution was passed through a column of Amberlite IR-120 resin (H^+ form) to remove glutamic acid. The eluate was evaporated to dryness and the syrupy *benzyloxycarbonyl* peptide (13 g., 55%) was dried over phosphoric oxide (Found: C, 53·8; H, 6·3; N, 8·4. $C_{16}H_{20}O_7N_2$ requires C, 54·3; H, 5·7; N, 8·0%). It had R_F 0·07 in butanol–acetic acid–water and contained a trace of benzyloxycarbonyl-β-alanine.

β-*Alanyl*-L-*glutamic Acid*.—The above benzyloxycarbonyl compound (11·5 g.) in methanol–acetic acid–water (44 : 3 : 3; 120 c.c.) was shaken with hydrogen in the presence of palladium. After hydrogenation was complete the catalyst was filtered off and the filtrate was evaporated to small volume *in vacuo*. Addition of alcohol precipitated an oil which on drying became a brittle, hygroscopic solid (6·5 g., 91%) (Found: C, 44·3; H, 6·7; N, 11·9. $C_8H_{14}O_5N_2$ requires C, 44·0; H, 6·4; N, 12·9%). The *peptide* had R_F 0·21 in butanol–acetic acid–water and contained a trace of β-alanine.

N-(D-*Pantothenoyl*)-L-*glutamic Acid*.—This was prepared from pantolactone (1·3 g.), β-alanyl-L-glutamic acid (21·7 g.), and dimethylamine (1·7 c.c.) in a manner similar to that described for pantothenoylglycine. The *dimethylamine* salt (3·5 g., 80%) had R_F 0·56 in butanol–acetic acid–water and contained a trace of pantothenic acid (Found: C, 49·2; H, 8·6; N, 12·9. $C_{14}H_{24}O_6N_2$ requires C, 49·3; H, 8·7; N, 12·8%).

*Benzyloxycarbonyl-β-alanyl-*DL*-α-alanine*.—A solution of benzyloxycarbonyl-β-alanine chloride (from 10 g. of benzyloxycarbonyl-β-alanine) in a little ether was added to a solution of alanine (4 g.) in 2N-sodium hydroxide (25 c.c.) at 0° with continuous addition of sodium hydroxide (to maintain slight alkalinity). After 1 hr. at room temperature the solution was acidified (Congo-red) and the crystalline precipitate collected. The *benzyloxycarbonyl* peptide recrystallised from water as plates, m. p. 142—143° (1·9 g.) (Found: C, 57·3; H, 6·4; N, 10·2. $C_{14}H_{18}O_5N_2$ requires C, 57·2; H, 6·1; N, 9·5%).

β-*Alanyl-*DL*-α-alanine*.—This was prepared by catalytic hydrogenolysis of the above benzyloxycarbonyl *peptide* (1·7 g.) as described for β-alanylserine. The *peptide*, m. p. 228—230° (0·9 g.), was homogeneous on paper chromatography in butanol–acetic acid–water (R_F 0·4) (Found: C, 41·3; H, 7·8; N, 15·4. $C_6H_{12}O_3N_2,H_2O$ requires C, 40·5; H, 7·9; N, 15·7%).

D-*Pantothenoyl-*DL*-α-alanine*.—This was obtained from pantolactone and β-alanyl-α-alanine by the method used for pantothenoylglycine. The *dimethylamine* salt had m. p. 132° after softening at 100° (Found: C, 50·1; H, 8·8; N, 12·3. $C_{14}H_{29}O_6N_3$ requires C, 50·2; H, 8·7; N, 12·5%).

D-*Pantothenamide*.—β-Alanine amide acetate was prepared by catalytic hydrogenation of benzyloxycarbonyl-β-alanine amide (Hanson and Smith, *loc. cit.*) under conditions similar to those described for the preparation of β-alanyl-DL-serine. The acetate (1·5 g.), D(−)-pantolactone (1·3 g.), and dimethylamine (1 c.c.) were refluxed together in methanol (10 c.c.) for 8 hr. Solvent was distilled off and an aqueous solution of the residue passed through a column of Amberlite IRC-50 resin (H^+ form), then Amberlite IR-4B (OH^- form). The neutral eluate was washed with ether and evaporated to dryness under reduced pressure. The glassy *product* (2 g.) had R_F 0·60 in butanol–acetic acid–water (Found: C, 49·1; H, 8·8; N, 12·7. Calc. for $C_9H_{18}O_4N_2$: C, 49·5; H, 8·3; N, 12·8%). Traces of contaminants, R_F 0·35 and 0·88, were observed.

2-D-*Pantothenamidoacetaldehyde Diethyl Acetal*.—To a solution of the mixed anhydride, prepared from sodium pantothenate (4·82 g.) and ethyl chloroformate (1·95 c.c.) in dioxan (20 c.c.), was added aminoacetaldehyde diethyl acetal (2·66 g.) in dioxan (10 c.c.). The mixture was kept at 0° for 5 min., then allowed to warm to room temperature. The solvent was evaporated under reduced pressure and an aqueous solution of the residue passed through a column of Amberlite IR-4B resin (OH^- form), then through Amberlite IR-120 resin (H^+ form). The neutral, halogen-free effluent was evaporated to dryness, leaving a syrup (3·8 g., 57%) (Found: C, 53·6; H, 8·9; N, 8·6; OEt, 25·8. $C_{15}H_{30}O_6N_2$ requires C, 53·8; H, 9·0; N, 8·4; OEt, 26·9%). The *acetal* was homogeneous on paper chromatography in butanol–pyridine–water (R_F 0·94) and in butanol–acetic acid–water (R_F 0·84). It was detected on the paper by Rydon and Smith's method (*loc. cit.*) or by spraying with 0·1N-hydrochloric acid, heating at 100° for 5 min., then spraying with Schiff's reagent. The acetal gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 114—115° (from alcohol) (Found: C, 46·0; H, 5·7; N, 18·7. $C_{17}H_{24}O_8N_6$ requires C, 46·3; H, 5·5; N, 19·1%).

2-D-*Pantothenamidoacetaldehyde*.—Qualitative experiments indicated that, although the above acetal did not reduce ammoniacal silver nitrate, rapid reduction was observed on samples which had been boiled with N-hydrochloric acid for 1 min. Paper chromatography of hydrolysates established that the acetal (R_F 0·94 in butanol–pyridine–water, 0·84 in butanol–water) was completely converted into the aldehyde (R_F 0·77 in butanol–pyridine–water, 0·60 in butanol–water) when heated at 100° for 2 min. in water containing a trace of sulphuric acid. The aldehyde appeared as a brown spot on paper after spraying with ammoniacal silver nitrate and then heating at 100° for 2 min. The following method was adopted for preparing quantities of the aldehyde.

A solution of the acetal (1 g.) in water (100 c.c.) was acidified by adding 1 drop of 50% sulphuric acid and then boiled for 2 min. The solution was neutralised with barium hydroxide solution, filtered, and evaporated to dryness *in vacuo*. The residual syrup was dissolved in dry alcohol and D-*pantothenamidoacetaldehyde* was precipitated as a white solid by addition of dry ethyl acetate and ether in almost quantitative yield (Found: C, 50·2; H, 8·2; N, 10·3. $C_{11}H_{20}O_5N_2$ requires C, 50·7; H, 7·7; N, 10·8%).

Oxidation to D-*Pantothenoylglycine*.—A solution of the aldehyde, prepared as above from

the acetal (0·167 g.), in water (2 c.c.) was treated with freshly prepared silver oxide (from 0·085 g. of silver nitrate) and sodium hydrogen carbonate (0·042 g.). The mixture was heated on a steam-bath with constant stirring for 4 hr. The solution was filtered and passed through a column of Amberlite IR-120 resin (H^+ form), and the acidic eluate evaporated to dryness *in vacuo*. Paper chromatography of the residue showed that the main product was indistinguishable from pantothenoylglycine (R_F 0·63 in butanol–acetic acid–water) prepared by the first method. Two slow-moving contaminants were observed.

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The Electrochemistry of Solutions of Hydrogen Chloride in Acetone: the Cell $H_2|HCl|Ag,AgCl$.

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A study has been made at 25° of the cell $H_2|HCl|Ag,AgCl$, pure acetone being used as solvent. Reproducible e.m.f.s were obtained which vary with the concentration of hydrogen chloride in a way which indicates that hydrogen chloride is a very weak acid in this solvent. Evidence is presented that its dissociation constant is about 10^{-8}. On this basis the standard potential of the silver–silver chloride electrode in acetone is about −0·53 v (cf. +0·2222 v in water). The solubility of silver chloride in acetone being taken as 4×10^{-18} mole/l., this leads to a standard potential of the silver electrode of about +0·50 v (cf. +0·798 v in water).

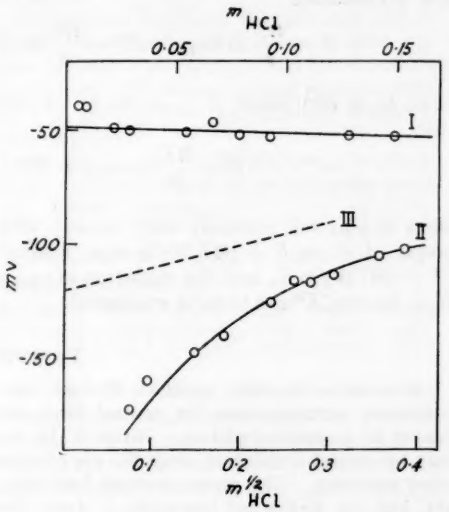
THE literature on the electrochemistry of non-aqueous solutions is extensive, but the majority of papers deal with conductivity measurements. Little work has been concerned with e.m.f. determinations and few cells without liquid junction have been investigated. The cell $H_2|HCl|Ag,AgCl$ has been studied, the following solvents being used: methanol (Nonhebel and Hartley, *Phil. Mag.*, 1925, **50**, 729), ethanol (Woolcock and Hartley, *ibid.*, 1928, **5**, 1133), dioxan + water (Harned, Walker, and Calmon, *J. Amer. Chem. Soc.*, 1939, **61**, 44), glycerol + water (Lucasse, *Z. physikal. Chem.*, 1926, **121**, 254), acetone + water (Izmailov and Zabara, *J. Phys. Chem. U.S.S.R.*, 1946, **20**, 165), and glacial acetic acid (Heston and Hall, *J. Amer. Chem. Soc.*, 1934, **56**, 1462). In the last two investigations quinhydrone and chloranil electrodes, respectively, were used in place of the H_2–Pt electrode. There is no report of measurements of this cell when pure acetone is used as solvent.

A study of metal–metal halide electrodes in acetone solutions has been made by Ulich and Spiegel (*Z. physikal. Chem.*, 1936, **177**, *A*, 103), who report that most of them give irreproducible and unstable potentials. They explain this by supposing that complex ions of the type $M_mCl_n^{(n-m)-}$ are formed: qualitative support for this comes from the observation that the solubilities of silver and mercury halides in acetone are increased by the addition of lithium halide. In our experience, however, silver–silver chloride electrodes when prepared carefully behave satisfactorily in acetone.

Nature of Hydrogen Chloride + Acetone Solutions.—Evidence regarding the state of hydrogen chloride in acetone is conflicting. The early conductivity work of Sackur (*Ber.*, 1902, **27**, 326) suggests that hydrogen chloride behaves as a strong electrolyte, and the same conclusion is reached by Braude (*J.*, 1948, 1971) on the basis of spectrophotometric measurements of the "acidity function" in acetone. On the other hand, conductivity measurements carried out by Ross Kane (Thesis, Oxford, 1929; cf. *Ann. Reports*, 1930, **27**, 344) indicated that hydrogen chloride behaves as a very weak acid

($K_a \sim 10^{-8}$) in acetone. His results were not, however, very reproducible and the work was not published in full. Some preliminary measurements by Mackor (personal communication) confirm the difficulty of obtaining reproducible results, but indicate a dissociation constant of 10^{-6}; Mackor also suggests that his results may indicate the dimerization of hydrogen chloride in acetone. Recent conductivity measurements by Dr. M. J. Sparnaay in this laboratory confirm that hydrogen chloride does not behave as a simple acid in acetone, but that other equilibria are involved. Nevertheless, the ionic concentrations in the solution correspond approximately to those which would be derived from a weak acid of K_a in the range 10^{-8} to 10^{-7}.

An independent value may be obtained by studying the solubility of silver chloride in hydrogen chloride + acetone. The complexity constant* (K_c) for the reaction $AgCl + Cl^- \rightleftharpoons AgCl_2^-$ is given by Mackor (*Rec. Trav. chim.*, 1951, **70**, 457) as about 5, so that if hydrogen chloride were completely dissociated, silver chloride would be very



Curve I, $E + \frac{RT}{F} \ln m_{HCl}$ against m_{HCl}.

Curve II, $E + \frac{2RT}{F} \ln m_{HCl}$ against $m_{HCl}^{\frac{1}{2}}$.

Curve III, Theoretical slope of curve II at infinite dilution.

soluble in hydrogen chloride + acetone: this is not so. Hydrogen chloride being assumed to be a weak acid in acetone, the solubility of silver chloride is given, approximately, by the equation

$$m_{AgCl_2^-} = \{[K_c^2/(K_c + 1)]m_{HCl}K_a\}^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where m_{HCl} is the stoicheiometric (initial) concentration of hydrogen chloride.

A number of experiments were carried out in an attempt to determine $m_{AgCl_2^-}$. In these, crystals of silver chloride were sealed in tubes containing hydrogen chloride + acetone of known strength (about N/10) and rotated in a thermostat at 25° for several days. The ampoules were then opened, and a sample of the solution diluted with an equal volume of conductivity water. The formation of an opalescence, and the eventual coagulation of the precipitate, was followed in a Hilger Spekker Absorptiometer. Calibration experiments were carried out by adding known volumes of 0·01N-silver nitrate solution to solutions of hydrogen chloride in 50% acetone + water. In all cases the opalescence increased to a maximum and then declined linearly with time. The observations were not easily reproducible, for the opalescence produced in the solubility determinations gave optical densities of the order of only 0·05. These were matched in calibration runs in which the silver-ion concentration was about 3×10^{-5}. From these experiments we conclude that the solubility of silver chloride in 0·1*m*-hydrogen chloride in

* The complexity constant is defined as the equilibrium constant for the formation of a complex ion.

acetone is $3{\cdot}0 \pm 1{\cdot}0 \times 10^{-5}$. It was found also that some reaction occurred in the solution in the course of several days at 25°, leading to a slight yellow coloration and the development of a characteristic odour. Equilibration for less than 48 hr., however, gave an undetectable quantity of silver ion in the solution. Despite the large experimental uncertainty of these measurements, they indicate that the order of magnitude of the acid dissociation constant of hydrogen chloride in acetone is between 10^{-8} and 10^{-9}.

The Cell $H_2|HCl|Ag,AgCl$ *in Acetone.*—The e.m.f. of this cell is given by

$$E = E^0 - (2RT/F) \ln \alpha m_{HCl} \gamma_{\pm} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where α is the degree of dissociation, m_{HCl} the stoicheiometric molality of hydrogen chloride, and $\gamma_{\pm}$ the mean activity coefficient of the ions. On introduction of the dissociation constant

$$K_a = m_{HCl} [\alpha^2/(1 - \alpha)] \gamma_{\pm}^2/\gamma_{HCl} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

eqn. (2) becomes

$$E + \frac{RT}{F} \ln m_{HCl} = E^0 - \frac{RT}{F} \ln K_a - \frac{RT}{F} \ln (1 - \alpha) - \frac{RT}{F} \ln \gamma_{HCl} \quad . \quad . \quad (4)$$

Since K_a is very small, $(1 - \alpha)$ can be set equal to unity at the concentrations studied, so that

$$E + \frac{RT}{F} \ln m_{HCl} = E^0 - \frac{RT}{F} \ln K_a - \frac{RT}{F} \ln \gamma_{HCl} \quad . \quad . \quad . \quad . \quad (5)$$

Since $\ln \gamma_{HCl}$ will probably vary linearly with m_{HCl} in dilute solution, we might expect a graph of $E' = E + (RT/F) \ln m_{HCl}$ against m_{HCl} to be linear. The intercept gives $E^0 - (RT/F) \ln K_a$ and the variation of γ_{HCl} with m_{HCl} can be deduced from the slope. If K_a is known, E^0 can then be evaluated.

Experimental

Materials.—Acetone, purified through the bisulphite compound, was kept over solid potassium permanganate for several days and fractionally distilled in an efficient column (about 40 theoretical plates). Water is the main impurity and can be removed satisfactorily only by careful distillation, since the use of strong dehydrating agents tends to lead to condensation reactions. The purest acetone has been reported (Lannung, *Z. physikal. Chem.*, 1932, **161**, 255; cf. Kraus and Reynolds, *J. Amer. Chem. Soc.*, 1948, **70**, 1709) to have a conductivity of 10^{-10} ohm^{-1} cm. at 20°; that used in the present work varied from batch to batch in the range $3—5 \times 10^{-9}$ ohm^{-1} cm.

Hydrogen chloride solutions in acetone were prepared by passing dry hydrogen chloride into acetone. The hydrogen chloride was made from dry, bromine-free sodium chloride and concentrated " AnalaR " sulphuric acid, and was passed through a trap at −70° and through anhydrous magnesium perchlorate before entering the acetone. The acetone + hydrogen chloride solution was analysed by weighing out a portion and pouring it into aqueous silver nitrate. The mixture was boiled gently for about ½ hr. and left for 3—4 days to ensure complete precipitation of the silver chloride, which was then collected in a sintered-glass crucible and weighed. Analyses were made both of the freshly prepared solution and of the solution at the end of the run. These usually agreed well.

Technique.—The silver–silver chloride electrodes consisted of an intimate mixture of precipitated silver and silver chloride as recommended by Brønsted (*Kgl. Danske Vidensk. Selsk.*, 1920, **3**, No. 9) and by Güntelberg (*Z. physikal. Chem.*, 1926, **123**, 199). Great care was taken to remove bromide impurities because of their serious effect on the potential of this electrode. The hydrogen electrodes were 1 cm.^{2} platinized platinum plates. Preliminary work by Mr. D. S. Brown in this laboratory had shown that hydrogen electrodes produce no detectable reduction of acetone to *iso*propyl alcohol during bubbling of hydrogen for 24 hr.

The cell was essentially similar to that described by Güntelberg and contained duplicate sets of electrodes. The solution in the silver–silver chloride electrode compartment was deoxygenated with oxygen-free nitrogen; this is very important because of the high solubility of oxygen in acetone and the effect of this gas on the potential of the electrode. Hydrogen from a cylinder was purified by passage over heated copper, then over soda–lime and through a

liquid-air trap. Gases were brought into equilibrium with the cell solutions by means of pre-saturators; to be effective these had to be of large volume (5 × the volume of the solution in the cell).

Because of the high resistance of the cell, an electrometer valve detector similar to that described by Greville and Maclagan (*Trans. Faraday Soc.*, 1931, **27**, 210) was used in conjunction with a Tinsley Type 4025 potentiometer. All leads were of coaxial-screened cable. E.m.f.s could be read to better than 0·1 mv. The cell was kept in a screened air-thermostat maintained at 25° ± 0·1°.

Before each run the cell and pre-saturators were washed several times with distilled water, then conductivity water and finally acetone. They were then dried for 36 hr. at 120°. Filling with solution was carried out by means of an apparatus which reduced contact between the solutions and air to a minimum. The electrodes reached equilibrium in 6—12 hr. and the e.m.f.s remained constant to within 0·5 mv for at least several hours. Equilibrium was always approached from lower values of the e.m.f., the hydrogen electrode becoming steadily more negative relative to the silver–silver chloride electrode.

As mentioned above, a slow reaction takes place between hydrogen chloride and acetone. Some preliminary unpublished work by Fletcher, Ogston, and Gatty (1934) (personal communication from Dr. A. G. Ogston) suggests that in 0·1N-solution at room temperature the reaction is approximately of first order with a half-life of some 350 hr. The constancy and reproducibility of the e.m.f.'s obtained in our work indicate that this reaction does not seriously affect the results, provided that freshly prepared solutions are employed.

Results.—The results are summarized in the Table and $E' = E + (\boldsymbol{RT/F}) \ln m_{HCl}$ is plotted against m_{HCl} in Curve I. Apart from the two points at concentrations below 0·01m the points lie, to within 2—3 mv, on the straight line $E'(\text{v}) = -0{\cdot}049 - 0{\cdot}02\, m_{HCl}$.

E.M.F. of the cell $H_2|HCl|Ag,AgCl$ *in pure acetone at* 25° ($p_{H_2} = 1$ atm.).

(Sign of e.m.f. is that of the right-hand electrode.)

m_{HCl}	0·0056	0·0090	0·0219	0·0290	0·055	0·067	0·079	0·093	0·128	0·149
E (mv)	+93·8	+81·1	+48·3	+39·2	+22·6	+22·6	+12·6	+7·2	−0·1	−4·6
$E + (\boldsymbol{RT/F}) \ln m_{HCl}$ (mv)	−39·4	−39·4	−49·8	−50·9	−51·8	−46·7	−52·4	−53·2	−52·9	−53·5

This is in accordance with the predictions of eqn. (5). If hydrogen chloride were a strong electrolyte in acetone a graph of $E + (2\boldsymbol{RT/F}) \ln m_{HCl}$ against $m_{HCl}^{\frac{1}{2}}$ should approach linearity at small concentrations and have a slope of 0·094. As shown in Curve II, this is not so. If we assume the dissociation constant of hydrogen chloride in acetone to be about 10^{-8}, we obtain for the standard potential of the silver–silver chloride electrode in acetone $E^0_{Ag,AgCl} = -0{\cdot}53$ v, compared with +0·2222 v in water.

Using Mackor's value (personal communication) for the solubility product of silver chloride in acetone, *viz.*, $L = 4 \times 10^{-18}$, we obtain for the standard potential of the silver electrode in acetone $E^\circ_{Ag} = +0{\cdot}50$ v, compared with +0·798 v in water. Silver is therefore much less " noble " in acetone than in water.

The slope of curve I should be $(2{\cdot}303\boldsymbol{RT/F}) \log \gamma_{HCl}$, which leads to $\log \gamma_{HCl} = 0{\cdot}3m$. We do not know of any other estimates of the activity coefficient of hydrogen chloride in acetone with which to compare this value.

The above estimates of standard potentials are, of course, dependent upon the accuracy of the rough value of 10^{-8} for K_a, and of Mackor's determination of the solubility of silver chloride in acetone.

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Constitution and Stereochemistry of the Kamlolenic Acids.

By L. Crombie and J. L. Tayler.

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Kamlolenic acid is a conjugated 18-hydroxyoctadecatrienoic acid. There is no evidence for the presence of a keto-group. The triene system is in the 9 : 11 : 13-position, since ozonolysis of the methyl ester gives methyl 8-formyloctanoate. Kamlolenic acid is thus (II). Infra-red and ultra-violet light-absorption data enable the stereochemistry of α- and β-kamlolenic acid to be equated with that of α- and β-elæostearic acid. The β-form is the all-*trans*-compound whilst the α-form is probably the *cis*-9 : *trans*-11 : *trans*-13-stereoisomer.

The fruit of *Mallotus philippinensis* Muell. Arg. (a member of the *Euphorbiacae*) has long been known as the source of a dye, rottlerin, which has anthelmintic and purgative properties, but only recently has the nature of the seed oil been investigated. This oil (kamala oil) has drying properties similar to those of tung oil (also obtained from a member of the *Euphorbiacae*), and as the small evergreen tree from which it comes is widely distributed in Asia it has potential commercial interest [Puntambekar, *Current Sci.*, 1942, **11**, 464; Krishna, Puntambekar, and Raizada, *Indian Forest Record* (*New Ser.*), 1936, **1**, 2]. Seeds examined by us contained 42% of kernel which yielded 30% of oil. An unstable unsaturated acid has been isolated from kamala oil and named α-kamlolenic acid (Aggarwal, Bhatnagar, Narain, and Karimullah, *J. Sci. Ind. Res., India*, 1948, **7***B*, 136; Gupta, "Proc. Symp. on Indian Oils and Fats and their Utilisation," 1951, p. 33). The present communication is concerned with its structure and stereochemistry.

On iodine-catalysed ultra-violet irradiation, α-kamlolenic acid, in light petroleum, is transformed into a less soluble stereoisomeric β-form with a higher melting point. When hydrogenated, both acids yield 18-hydroxyoctadecanoic acid and three mols. of hydrogen are absorbed (Gupta, Sharma, and Aggarwal, *J. Sci. Ind. Res., India*, 1951, **10**, *B*, 76; Gupta, *loc. cit.*). Our observations are in agreement with these facts and we are unable to support the view of Puntambekar (*Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 57) that α-kamlolenic acid is not a pure compound or that it contains a keto-group which is reduced to a hydroxylic function during hydrogenation. Thus, the infra-red spectra of both kamlolenic acids (and their methyl esters) show strong primary hydroxyl absorption bands in the OH stretching and bending regions (near 3200 and 1060 cm.$^{-1}$), whilst for the α-acid there is no indication of a C=O grouping beyond that formally derived from the carboxyl grouping. Furthermore, both methyl esters yield crystalline α-naphthylurethanes (Table 1) and recently Gupta, Gupta, and Aggarwal (*J. Sci. Ind. Res., India*, 1953, **12**, *B*, 240) described acetyl derivatives. The two acids form crystalline methyl and *p*-bromophenacyl esters.

Table 1.

Acid	Acid, m. p.	Micro-hydrog.	Me ester, m. p.	*p*-Bromophenacyl ester, m. p.	α-Naphthylurethane of Me ester, m. p.	Acetyl deriv., m. p.*
α-Kamlolenic	78°	2·9H_2	24°	86°	58°	43—44°
β-Kamlolenic	89	3·0H_2	45	96—98	61	58—59

* Data of Gupta *et al.* (*loc. cit.*).

Location of the triple unsaturation in the 18-hydroxyoctadecanoic chain has occasioned some confusion. Aggarwal *et al.* at first believed that kamlolenic acid was either the 18-hydroxy-9 : 12 : 14- or the -9 : 13 : 15-trienoic acid (see also Gupta, Sharma, and Aggarwal, *ibid.*, 1952, **11**, *B*, 463). Puntambekar (*loc. cit.*) favoured 3-oxo-5 : 7-diene or 8-oxo-9 : 11 : 13-triene structures but his degradative evidence does not warrant such conclusions. Very recently, Calderwood and Gunstone (*Chem. and Ind.*, 1953, 436) and Gupta, Gupta, and Aggarwal (loc. cit.) reported that kamlolenic acid absorbs ultra-violet light in the manner typical of a triene (see also Table 2), and yields azelaic acid on permanganate oxidation.

This confines the unsaturation to the 9 : 11 : 13- or 5 : 7 : 9-positions (II or I). A decision can now be made as methyl α-kamlolenate yields, on ozonolysis, the aldehyde-ester (III) which can come from (II) but not from (I). The aldehyde was isolated as its 2 : 4-dinitro-

TABLE 2. *Ultra-violet light absorption data* (*solvent* : *ethanol*).

	$\lambda_{max.}$ (mμ)	10^{-3} ε		$\lambda_{max.}$ (mμ)	10^{-3} ε
α-Kamlolenic acid [a]	261	40·5	β-Kamlolenic acid [a]	258	45·0
	271	52·0		268	60·0
	282	42·0		279	47·0
Methyl α-kamlolenate	261	38·0	Methyl β-kamlolenate ...	258	42·0
	270·5	49·0		268	57·0
	282	40·0		279	44·5
α-Elæostearic acid [b]	261	36·0	β-Elæostearic acid [b]	259	47·0
	271	47·0		268	61·0
	281	38·0		279	49·0

[a] Gupta, Gupta, and Aggarwal (*loc. cit.*) give max. at 270·5 (ε 53,000) and 268 mμ (ε 58,500) for the main band of the α- and β-acid respectively. [b] O'Connor and Heinzelman (*J. Amer. Oil Chem. Soc.*, 1947, **24**, 212) give 270 (ε 47,000) and 268 mμ (ε 60,300) for the main band of the α- and β-acid respectively.

phenylhydrazone and compared with an authentic specimen obtained by the ozonolysis of methyl oleate. Kamlolenic acid is thus 18-hydroxyoctadeca-9 : 11 : 13-trienoic acid and it remains to deal with its stereochemistry.

$HO{\cdot}[CH_2]_8{\cdot}[CH{=}CH]_3{\cdot}[CH_2]_3{\cdot}CO_2H$ (I) $\quad HO{\cdot}[CH_2]_4{\cdot}[CH{=}CH]_3{\cdot}[CH_2]_7{\cdot}CO_2H$ (II) $\quad OHC{\cdot}[CH_2]_7{\cdot}CO_2Me$ (III)

The ready α ⟶ β transformation is reminiscent of elæostearic and licanic acid and ultra-violet absorption data support the analogy. On passing from α-kamlolenic or α-elæostearic acid to the corresponding β-form, there is a similar shift of the triplet to slightly shorter wave-lengths and a similar increase in the extinction coefficients (Table 1). But on this evidence only the resemblance might be superficial. There are two other reported stereoisomers of the elæostearic structure—punicic acid from pomegranate oil (Toyama and Tsuchiya, *J. Soc. Chem. Ind., Japan*, 1935, **38**, 182B; Farmer and Van den Heuvel, *J.*, 1936, 1809), and the little-investigated trichosanic acid from the oil of *Trichosanthes cucumeriodes* (Toyama and Tsuchiya, *J. Soc. Chem. Ind., Japan*, 1935, **38**, 185B), which by stereomutation yield β-elæostearic acid and would certainly show a similar increase in extinction coefficient in the process. Further evidence was therefore sought from infra-red spectra.

Comparison of the spectra (paraffin mulls) of kamlolenic with elæostearic acids affords strong justification for equating the stereochemistry in the α- and β-forms. There is a remarkable similarity (Table 3) especially in the region 1000—700 cm.$^{-1}$, and this is of

TABLE 3. *Infra-red comparison at* 1000—700 *cm.*$^{-1}$.

Acid										
α-Kamlolenic	993 s	967 ms	932 ms	916 ms	875 w	818 w	783 w	768 w	747 ms	728 m
α-Elæostearic	991 s	967 ms	932 m	917 ms	874 w	822 w	784 w	767 w	747 ms	727 m
β-Kamlolenic	999 m	986 s	929 w	899 m	876 m	834 mw	766 w	—	730 m	719 m
β-Elæostearic	998 s	987 vs	929 w	899 m	877 m	833 mw	766 w	—	729 m	719 m

vs = very strong; s = strong; m = moderate; w = weak.

particular interest as regularities in the C=C–H out-of-plane bending region may prove useful for identification of trienes of unknown configuration. It is significant that the two β-acids have a doublet (near 1713 and 1702 cm.$^{-1}$) in the carboxylic C=O stretching region whilst the α-acids have but one resolvable maximum (1687 cm.$^{-1}$). This seems to be due to differing arrangements in the crystal (and hence of the hydrogen-bonding pattern), which are imposed by different geometrical stereochemistry.

Recent work by Paschke, Tolberg, and Wheeler (*J. Amer. Oil Chem. Soc.*, 1953, **30**, 97) indicates that β-elæostearic acid is the all-*trans*-9 : 11 : 13-isomer, whilst α-elæostearic acid is the *cis*-9 : *trans*-11 : *trans*-13-stereoisomer. On the basis of the arguments above, the same stereochemistry is assigned to α- and β-kamlolenic acids, though the reservation must

be made that the *trans*-9 : *trans*-11 : *cis*-13 might not be readily distinguishable from the *cis*-9 : *trans*-11 : *trans*-13 by any of the methods used. The placing of two *trans*-double bonds in a contiguous position in both molecules accords with the almost theoretical diene numbers of the acetylated acids (Gupta, Gupta, and Aggarwal, *loc. cit.*). The fact that the split C=C stretching vibrations are easier to detect in methyl α-kamlolenate than in methyl β-kamlolenate is in agreement with the higher symmetry of the latter molecule.

Experimental

Microanalyses were carried out in the microanalytical laboratories of Imperial College (Mr. F. H. Oliver).

Isolation of α- and β-Kamlolenic Acids.—Kamala kernels (50 g.) were crushed gently and continuously extracted with light petroleum (b.p. 40—60°) to give, on evaporation of the solvent, a clear yellow oil (15 g.). This was heated under reflux in nitrogen for 30 min. with ethanolic potassium hydroxide (10%; 100 ml.). After concentration *in vacuo*, the acids were isolated in the usual way. When these were set aside in ether at 0°, α-kamlolenic acid separated as white crystals: concentration yielded a second crop (total 3·5 g.; m.p. 72—75°). The acid was purified by recrystallisations from ether (Found: C, 73·5; H, 10·4. Calc. for $C_{18}H_{30}O_2$: C, 73·45; H, 10·25%). For further data see Tables.

α-Kamlolenic acid (2·0 g.) was dissolved in a mixture (200 ml.) of 1 : 1 light petroleum (b. p. 40—60°)–ether, and a trace of iodine was added. This solution was irradiated (3 hr.) at 20° (quartz flask) with ultra-violet light. β-Kamlolenic acid (1·0 g.; m. p. 87—88·5°) separated, and a further crop (0·25 g.) was isolated by concentration (Found: C, 73·55; H, 10·45%). Prolonged irradiation leads to the formation of oil.

Derivatives of α- and β-Kamlolenic Acids.—By treatment with diazomethane in ether, crystalline *methyl* esters were isolated. The α- (Found: C, 73·9; H, 10·45. $C_{19}H_{32}O_2$ requires C, 74·0; H, 10·45%) and the β-form (Found: C, 74·15; H, 10·5%) were purified by low-temperature crystallisation from pentane. These esters yielded *α-naphthylurethanes*. Both the α- (Found: C, 75·45; H, 8·3. $C_{30}H_{39}O_4N$ requires C, 75·45; H, 8·25%) and the β-urethanes (Found: C, 75·50; H, 8·4%) crystallised from light petroleum (b. p. 60—80° or 80—100°). Despite their similar m. p.s (Table 1) these were depressed by more than 8° on admixture.

p-*Bromophenacyl* esters were isolated in the usual way and crystallised from ethanol (Found: α-Form: C, 63·5; H, 7·3. β-Form: C, 63·6; H, 7·2. $C_{26}H_{35}O_4Br$ requires C, 63·55; H, 7·2%).

The two acids react with maleic anhydride in benzene at 100° but the products are not easily purified since reaction seems to occur at the hydroxyl grouping as well as with the dienic system.

α- and β-Elæostearic Acids.—The α-acid (m. p. 47·5°) was purified by low-temperature crystallisation from pentane (Found: C, 77·5; H, 11·0. Calc. for $C_{18}H_{30}O_2$: C, 77·65; H, 10·85%). The β-acid (m. p. 72°) was similarly purified (Found: C, 77·4; H, 10·9%).

Hydrogenation of α-Kamlolenic Acid.—The acid (105 mg.), dissolved in ethyl acetate (10 ml.), was added to pre-reduced palladium–carbon (100 mg.) in ethyl acetate (10 ml.). Hydrogen (3 mols.) was absorbed at atmospheric pressure. The catalyst was removed by filtration and washed with hot ethyl acetate. Cooling of the filtrate gave 18-hydroxystearic acid (60 mg.) which when twice recrystallised from ethyl acetate had m. p. 98° (Chuit and Hausser, *Helv. Chim. Acta*, 1929, **12**, 463, give m. p. 96·6—97·2°).

Ozonisation of Methyl α-Kamlolenate.—Ozonised oxygen was bubbled through a solution of methyl α-kamlolenate (1·26 g.) in glacial acetic acid (15 ml.) until the solution no longer decolourised bromine in acetic acid. Ether (15 ml.) and zinc dust (1·5 g. in portions) were added, together with a few drops of water, and the mixture was refluxed gently until it no longer reacted with starch–iodide paper. The solid was removed by filtration and washed with ether, and the united ethereal extracts were washed with water. The ether was removed under reduced pressure, the residue dissolved in ethanol (20 ml.), and 2 : 4-dinitrophenylhydrazine (800 mg.) added. After addition of concentrated hydrochloric acid (1 ml.) to the boiling solution, heating was maintained for 2 min. and the mixture cooled (0°) for 18 hr. The orange crystals were filtered off and extracted with benzene. Evaporation of the ethanolic filtrate gave a red material which was also extracted with benzene. The two extracts were washed, dried, evaporated, and chromatographed on alumina. At least nine bands were formed but attention was confined to those more easily eluted. The first three fractions were oily and semisolid (250 mg.) and the later ones oils or glues. Fraction 2 (80 mg.) was washed with a little ethanol and yielded a yellow crystalline solid containing traces of orange material (45 mg.). This was crystallised five times from ethanol and had m. p. 64—65° (Found: C, 52·3, 53·05; H, 6·4, 6·4; N, 14·75%), un-

depressed on admixture with an authentic specimen of the 2 : 4-dinitrophenylhydrazone of methyl 8-formyloctanoate (see below).

Methyl 8-Formyloctanoate.—Methyl oleate was purified by distillation through a Stedman gauze-packed column : we are indebted to Mr. R. Ackman, Mr. B. W. Baker, and Mr. A. G. Jacklin for this purification. The ester (2·2 g.) was ozonised as described above and gave a mixture of 2 : 4-dinitrophenylhydrazones (2·2 g.). Chromatography of the mixture (1 g.) on alumina gave crude nonaldehyde 2 : 4-dinitrophenylhydrazone in the first benzene fractions (630 mg. crude; 330 mg. pure, m. p. 103—105°). The next group of fractions gave the crude 2 : 4-*dinitrophenylhydrazone* of methyl 8-formyloctanoate (250 mg. crude; m. p. 66·5°, pure). This crystallised from ethanol as yellow needles (Found : C, 52·25; H, 6·05; N, 15·35. $C_{16}H_{22}O_6N_4$ requires C, 52·45; H, 6·05; N, 15·3%).

Ultra-violet Light Absorption Data.—These were determined with a Unicam photoelectric instrument immediately after dissolution of the sample in ethanol. Solutions kept for a few hours showed a marked decline in extinction coefficient. The solid kamlolenic acids themselves are stable at 0° in stoppered tubes for at least one week (m.p. and light absorption) but deteriorate after some days at 20°. The α-methyl ester sealed under nitrogen became very resinous after 18 hr. at 20°.

*Infra-red Spectra.** —The spectra of α- (C.S. no. 128) and β-kamlolenic acid (C.S. no. 129), the β-methyl ester (C.S. no. 130) and α- (C.S. no. 131) and β-elæostearic acid (C.S. no. 132) are deposited with the Chemical Society. We are indebted to Dr. W. C. Price for the use of a single-beam Grubb–Parsons spectrometer (rock salt optics).

We are grateful to Professor R. P. Linstead, C.B.E., F.R.S., for his interest and to Dr. S. V. Puntambekar of the Forest Research Institute, Dehra Dun, for a generous supply of *Mallotus philippinensis* seeds.

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The Preparation of o-, m-, *and* p-*Alkoxy- and -Phenoxy-methylbenzy Chlorides.*

By Frederick G. Mann and Frederick H. C. Stewart.

[Reprint Order No. 5239.]

Several members of the above series of compounds, particularly in the *o*- and the *m*-series, were required for the investigation recorded in the following paper, and the comparative value of various synthetic routes has therefore been critically examined.

For the investigation described in the following paper several *o*-, *m*-, and *p*-alkoxy- and -phenoxy-methylbenzyl chlorides were required. The present paper affords a critical discussion of various syntheses of these compounds, more particularly in the *ortho*- and *meta*-series : their general properties are also described, except that their reaction with magnesium is reserved for the following paper.

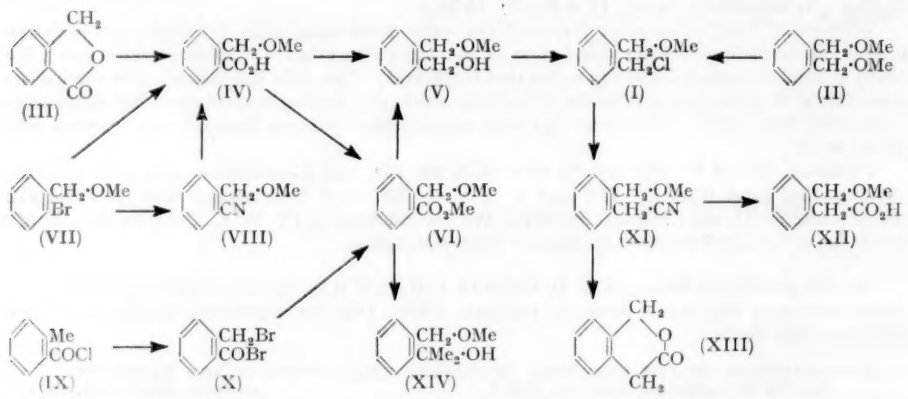
o-Methoxymethylbenzyl chloride † (I) was prepared in a crude condition by Murahashi (*Sci. Papers Inst. Phys. Chem., Tokyo,* 1936, **30**, 180), who converted *o*-xylylene dibromide, $C_6H_4(CH_2Br)_2$, into *o*-xylylene dimethyl ether (II), which when treated with acetyl chloride and a trace of zinc chloride afforded the chloride (I), this selective demethylation being an application of that used earlier by Quelet (*Compt. rend.*, 1931, **192**, 1391) in the *para*-series. We find that the chloride (I) thus obtained and fractionally distilled, although of sufficiently high quality for use in certain syntheses, cannot be obtained pure, as it is always contaminated by unchanged ether (II) of almost identical b. p. This little known but potentially useful method of partial demethylation suffers generally from this difficulty

* Photocopies may be obtained from the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1, on application quoting the C.S. numbers, price 3*s.* 0*d.* per copy, post free.

† This compound must be handled with great care. Not only is it strongly lachrymatory, but exposure to the vapour even at very high dilution at room temperature may cause visual derangement, headache, and gastric disturbance.

which could however probably be overcome by hydrolysing the chloride, *e.g.*, (I) to the alcohol (V), purifying the latter, and reconverting it into the chloride, or by the use of a higher alkyl homologue of the ether (II), the b. p. of which would differ from that of the chloride (as I). These possibilities were not, however, investigated in the present case in view of the following ready synthesis.

Phthalide (III) in alkaline solution, when treated with dimethyl sulphate, affords *o*-methoxymethylbenzoic acid (IV) which on reduction with lithium aluminium hydride gives *o*-methoxymethylbenzyl alcohol (V) : a higher yield of the alcohol is obtained if the acid is converted into the methyl ester (VI) before reduction. The alcohol (V) can then



be converted into the chloride (I) and the bromide (as I) by reaction with thionyl chloride and bromide respectively.

Alternative preparations of the acid (IV) and the ester (VI) have been examined. *o*-Bromobenzyl methyl ether (VII) (Holliman and Mann, *J.*, 1947, 1634) requires the " entrainment " method for adequate conversion into a Grignard reagent, and the latter on carboxylation gives the acid (IV) in only 13% yield. It is noteworthy that Mann and Millar (unpublished work) have found that this Grignard reagent also undergoes very little reaction with paraformaldehyde. This and related observations recorded below find a rational explanation on the assumption that the inertness is due to co-ordination of the oxygen to the magnesium atom, the reagent being stabilised by the five-membered ring so formed. The ether (VII), however, when heated with cuprous cyanide and pyridine at 215—225°, is converted into *o*-methoxymethylbenzonitrile (VIII) in 75% yield, and alkaline hydrolysis then furnishes the acid (IV) in 72% yield.

To prepare the ester (VI), *o*-toluoyl chloride (IX) was converted by the action of bromine into ω-bromo-*o*-toluoyl bromide (X) (Davies and Perkin, *J.*, 1922, **121**, 2202), which with sodium methoxide gave the ester (VI) in 80% yield. These alternative routes are however inferior to that from phthalide.

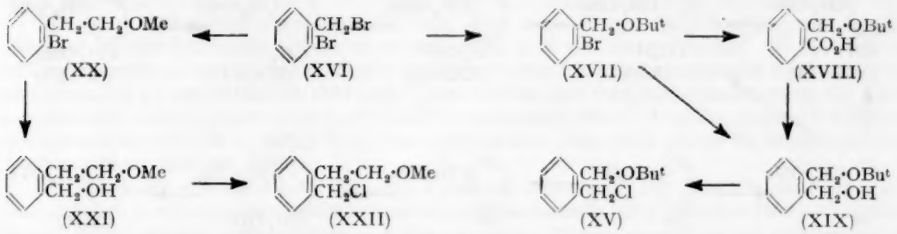
o-Methoxymethylbenzyl bromide (as I) is less stable than the chloride, and undergoes slight decomposition on distillation even at reduced pressure : for characterisation, the bromide and the chloride were heated with aqueous-ethanolic potassium cyanide to give the cyanide (XI), which on alkaline hydrolysis gave crystalline *o*-methoxymethylphenylacetic acid (XII) but on acidic hydrolysis readily gave 3 : 6-dihydro-4 : 5-benzo-2-pyrone (XIII).

The chloride (I) with sodium iodide in acetone readily gives the iodide, which could not be obtained pure by distillation, as this process caused considerable conversion into *o*-xylylene di-iodide.

2-*o*-Methoxymethylphenylpropan-2-ol (XIV), which was required for subsequent work, was prepared by the action of an excess of methylmagnesium iodide on the ester (VI) : it has considerable stability and can be distilled without decomposition.

To prepare *o*-phenoxymethylbenzyl chloride (as I), *o*-bromobenzyl bromide was

converted into *o*-bromobenzyl phenyl ether, the Grignard reagent from which on carboxylation gave *o*-phenoxymethylbenzoic acid (as IV) in 35% yield. This Grignard reagent, like that prepared from (VII), could also form an internal chelated complex, but the co-ordination of the oxygen of the phenoxyl group to the magnesium would probably be



weaker than that of the methoxyl group, and this would account for the higher yield of the phenoxy-acid (as IV). This acid was reduced as before to the alcohol (as V), and thence gave the required chloride.

For the investigation described in the following paper two types of homologues of the chloride (I) were required, in which the methyl group was replaced by (*a*) a *tert.*-butyl group (XV) and (*b*) a 2-methoxyethyl group (XXII).

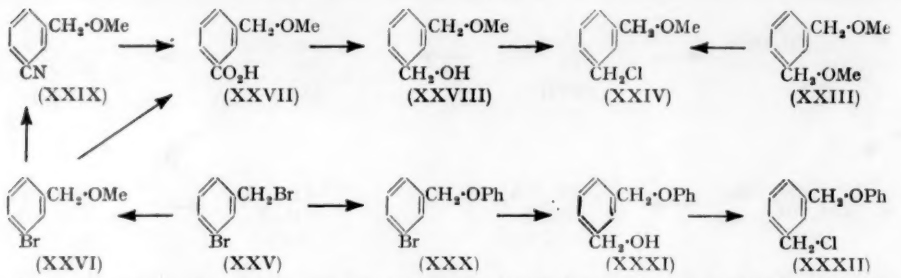
To prepare *o-tert.*-butoxymethylbenzyl chloride (XV), *o*-bromobenzyl bromide (XVI) was treated with sodium *tert.*-butoxide in the presence of benzene to give *o*-bromobenzyl *tert.*-butyl ether (XVII): in the absence of benzene, di-*o*-bromobenzyl ether was also formed. In the Grignard reagent from the bromo-ether (XVII) stabilisation by internal co-ordination was apparently largely prevented by the steric hindrance of the *tert.*-butyl group, for treatment with carbon dioxide gave *o-tert.*-butoxymethylbenzoic acid (XVIII) in 50% yield, and with formaldehyde gave *o-tert.*-butoxymethylbenzyl alcohol (XIX): the latter was also obtained by the lithium aluminium hydride reduction of the acid (XVIII). The action of thionyl chloride on the alcohol (XIX) then gave the required chloride (XV), an odourless non-lachrymatory liquid in marked contrast to (I).

The *o*-bromobenzyl bromide (XVI) was also converted by the method of Mann and Millar (*J.*, 1951, 2205) into 2-*o*-bromophenylethyl methyl ether (XX), the Grignard derivative of which, treated with formaldehyde, gave *o*-2-methoxyethylbenzyl alcohol (XXI) in 62% yield, and thence as usual the chloride (XXII). It seems significant also that carboxylation of this Grignard derivative gave *o*-2-methoxyethylbenzoic acid in 56% yield, for this Grignard reagent, if it underwent internal co-ordination, would form a six-membered and not a five-membered ring.

In the *para*-series, Quelet's reaction (*loc. cit.*), whereby *p*-xylylene dimethyl ether (as II) is treated with acetyl chloride containing zinc chloride, afforded a ready route to *p*-methoxymethylbenzyl chloride. Again, however, the chloride was contaminated with the unchanged dimethyl ether of almost identical b. p. Attempts to hydrolyse the chloride to the alcohol, in the hope that the latter could then be purified, proved unsatisfactory in this series. However the presence of the dimethyl ether did not affect our subsequent use of the chloride.

In the *meta*-series, two synthetic routes similar to those employed in the *ortho*-series proved of value. *m*-Xylylene dibromide was converted into the dimethyl ether (XXIII), which with acetyl chloride and zinc chloride gave *m*-methoxymethylbenzyl chloride (XXIV); this chloride, as in the two previous series, was not obtained pure but was nevertheless suitable for our subsequent purposes. To prepare the pure chloride (XXIV), however, *m*-bromobenzyl bromide (XXV) was converted into *m*-bromobenzyl methyl ether (XXVI), the Grignard reagent of which on carboxylation gave a 30% yield of *m*-methoxymethylbenzoic acid (XXVII) and thence the alcohol (XXVIII) and the chloride (XXIV). However, the alternative route *via* the nitrile (XXIX) again proved more efficient. It is significant that *m*-methoxymethylbenzyl chloride (XXIV) is an almost odourless liquid, apparently devoid of all the unpleasant physiological properties of the *o*-isomer (I).

The bromide (XXV) was similarly converted into *m*-bromobenzyl phenyl ether (XXX), the Grignard reagent of which with paraformaldehyde gave *m*-phenoxymethylbenzyl alcohol (XXXI), which in turn furnished the almost odourless chloride (XXXII). This



chloride was characterised by conversion into the nitrile and crystalline *m*-phenoxymethylphenylacetic acid.

Experimental

All compounds were colourless unless otherwise described. The yields recorded are those of products once distilled or recrystallised. The magnesium for Grignard reagents was activated as described by Holliman and Mann (*J.*, 1942, 739), but fine turnings were used to avoid the highly pyrophoric nature of the powdered metal. In addition, the "entrainment method" using ethyl bromide was employed when necessary to facilitate formation of the Grignard reagent.

o-*Methoxymethylbenzyl Chloride* (I).—The following preparation is based on Murahashi's directions (*loc. cit.*). Anhydrous zinc chloride (*ca.* 0·01 g.) was added to a mixture of the ether (II) (20 g.), acetyl chloride (6·6 g., 0·65 mol.), and carbon tetrachloride (16 c.c.). The stirred solution slowly became dark red as its temperature rose markedly. When cool, it was diluted with water and extracted with ether. Fractional distillation of the dried extract gave the lachrymatory chloride (I), b. p. 112—114°/13 mm. (14 g.). Analysis indicated that it contained *ca.* 55% of (I).

o-*Methoxymethylbenzoic Acid* (IV).—(*a*) Methyl sulphate (225 g., 6 mols.) was slowly added to a stirred chilled solution of phthalide (40 g.) in 20% aqueous sodium hydroxide (700 c.c.). After being stirred for 30 min., the mixture was heated on the water-bath to hydrolyse unchanged sulphate. The cold solution was acidified, and the precipitated acid (IV) collected and extracted with sodium carbonate solution; the extract, filtered from residual phthalide and then acidified, deposited the acid, m. p. 92—93°, sufficiently pure for further synthetic work.

(*b*) A solution of *o*-bromobenzyl methyl ether (VII) (60 g.) and ethyl bromide (32 g., 1 mol.) in ether (120 c.c.) was added to magnesium (15 g., 2·1 atoms) under ether (30 c.c.) so that gentle boiling ensued. The mixture was then boiled under reflux for 2 hr., cooled, and poured on an excess of solid carbon dioxide. After evaporation of the dioxide, the solution was treated with dilute hydrochloric acid, and extracted with more ether. The ether was then extracted with aqueous sodium carbonate, which on acidification deposited the acid (IV), m. p. 95—96° after recrystallisation from light petroleum (b. p. 80—100°) (Found: C, 65·3; H, 6·2. Calc. for $C_9H_{10}O_3$: C, 65·0; H, 6·0%) (6·5 g., 13%). Von Braun, Anton, and Weissbach (*Ber.*, 1930, **63**, 2861) give m. p. 93—94°.

Addition of copper sulphate to the sodium salt of (IV), each in aqueous solution, precipitated the *copper* salt, bluish-green crystals from ethanol–benzene (Found: C, 55·6; H, 4·9. $C_{18}H_{18}O_6Cu$ requires C, 55·0; H, 4·6%).

(*c*) A mixture of the ether (VII) (80 g.), cuprous cyanide (35·5 g.), and pyridine (55 c.c.) was heated at 215—225° for 15 hr., cooled, and poured into aqueous ammonia (*d* 0·88; 250 c.c.) diluted with water (250 c.c.). The mixture was then extracted with benzene and ether, and the united extracts were washed in turn with aqueous ammonia, dilute hydrochloric acid, and water. Distillation after drying gave *o*-methoxymethylbenzonitrile (VIII), b. p. 118—121°/15 mm. (44 g., 75%). Von Braun and Zobel (*Ber.*, 1923, **56**, 690) give b. p. 114°/14 mm.

Hydrolysis. (*a*) A mixture of the nitrile (VIII) (11 g.), ethanol (30 c.c.), and 10% aqueous sodium hydroxide (150 c.c.) was boiled under reflux for 2 hr., cooled, acidified, and extracted

with ether. The extract furnished the acid (IV), m. p. 95—96° alone and mixed, after recrystallisation (9·0 g., 72%).

A mixture of the nitrile (VIII) (3 g.), concentrated sulphuric acid (10 c.c.), and water (6 c.c.) was boiled under reflux for 30 min., cooled, and diluted with water. The precipitated crystalline phthalide (III) had m. p. 72·5—73° alone and mixed, after recrystallisation from light petroleum (b. p. 60—80°).

Methyl o-*Methoxymethylbenzoate* (VI).—(*a*) This ester, b. p. 126°/15 mm., was readily obtained by the interaction of the silver salt of the acid and methyl iodide. (*b*) ω-Bromo-*o*-toluoyl bromide (X) (65 g.) was gradually added to a chilled solution obtained by the interaction of sodium (12 g.) and methanol (350 c.c.). The mixture was then boiled under reflux for 1 hr., concentrated, cooled, poured into water, and extracted with ether. Distillation gave the almost odourless ester (VI) (28 g., 80%), b. p. 124—125°/15 mm., the value quoted by Staudinger and Mächling (*Ber.*, 1916, **49**, 1976).

o-*Methoxymethylbenzyl Alcohol* (V).—(*a*) A solution of the acid (IV) (33 g.) in ether (300 c.c.) was added to a stirred suspension of lithium aluminium hydride (12 g.) in ether (360 c.c.) so that steady boiling ensued. The mixture was then stirred for 30 min., cooled, mixed with ice-water, and finally shaken with dilute sulphuric acid. The dried ethereal layer on distillation gave the oily *alcohol* (V) (20 g., 66%), b. p. 132°/13 mm., 154—156°/35 mm. (Found: C, 71·2; H, 7·9. $C_9H_{12}O_2$ requires C, 71·0; H, 7·8%).

(*b*) The alcohol (12·1 g., 80%) was similarly obtained by the reduction of the ester (VI) (17 g.) with the hydride (3 g.) in ether (80 c.c. and 140 c.c. respectively).

o-*Methoxymethylbenzyl Chloride* (I).—A solution of thionyl chloride (16·2 g.) in chloroform (36 c.c.) was added during 1 hr. to a chilled stirred solution of the alcohol (V) (20·8 g.) and pyridine (10·8 g.) in chloroform (85 c.c.), and the mixture was then boiled under reflux for 2 hr. The cold solution was added to much water and extracted with ether; the extract was washed repeatedly with water and then with a 1% aqueous solution of sodium hydroxide. Fractional distillation gave the mobile *chloride* (I) (19·3 g., 82%), b. p. 114—116°/13 mm., 144°/42 mm. (Found: C, 63·7; H, 6·3. $C_9H_{11}OCl$ requires C, 63·4; H, 6·4%).

o-Methoxymethylbenzyl bromide (as I), b. p. 126—127°/16 mm., was similarly prepared in 63% yield by using freshly distilled thionyl bromide (Mayes and Partington, *J.*, 1926, 2594), as an intensely lachrymatory, colourless liquid, the vapour of which caused marked irritation of the skin. Since however it underwent partial decomposition when distilled even under reduced pressure, it was characterised by treatment with potassium cyanide in hot aqueous ethanol, whereby the nitrile (XI), b. p. 155—156°/17 mm., was obtained in 70% yield (Found: C, 74·3; H, 6·6; N, 8·6. Calc. for $C_{10}H_{11}ON$: C, 74·5; H, 6·8; N, 8·7%).

Hydrolysis of the Nitrile (XI).—(*a*) The nitrile (2·2 g.), when heated with ethanol (5 c.c.) and 10% aqueous sodium hydroxide (35 c.c.), followed by acidification, gave the acid (XII), m. p. 52—53° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 66·6; H, 6·5. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·6%). Murahashi (*loc. cit.*) gives b. p. 151—153°/17 mm. and m. p. 52—54° for (XI) and (XII) respectively.

(*b*) The mixture obtained by the addition of the nitrile (10 g.) to concentrated sulphuric acid (100 c.c.) previously diluted with water (400 c.c.) was boiled under reflux with stirring for 6 hr. and then further diluted with water and cooled, whereupon 3 : 6-dihydro-4 : 5-benzo-2-pyrone (XIII) crystallised (8 g., 87%); it had m. p. 81—82° after recrystallisation from water (Found: C, 72·8; H, 5·2. Calc. for $C_9H_8O_2$: C, 73·0; H, 5·4%). The use of more concentrated sulphuric acid gave an alkali-soluble resin as the sole product.

In an attempt to prepare the iodide (as I), the chloride (5 g.) was added to a solution of sodium iodide (4·5 g.) in acetone (30 c.c.). The red solution was set aside overnight, and when filtered and distilled gave the crude iodide as a yellow lachrymatory oil, b. p. 89—93°/0·3 mm. (5·4 g.), which readily became red. Redistillation caused partial decomposition, and gave a residue of *o*-xylylene di-iodide, m. p. 108—109° (alone and mixed) after crystallisation from ethanol (Found: C, 27·4; H, 2·9. Calc. for $C_8H_8I_2$: C, 27·0; H, 2·2%).

2-o-*Methoxymethylphenylpropan*-2-*ol* (XIV).—A solution of methyl *o*-methoxymethylbenzoate (VI) (8·2 g.) in ether was added slowly to the cooled stirred Grignard reagent prepared from methyl iodide (12·7 g.) and magnesium (2·2 g.) in ether (35 c.c.). The product was set aside overnight, cooled, and hydrolysed with dilute sulphuric acid. The oil obtained by the evaporation of the ether layer was added to a solution of potassium hydroxide (2·4 g.) in methanol (20 c.c.), which was boiled for 15 min., poured into water, and extracted with ether. Distillation of the extract gave the *alcohol* (XIV) (5·7 g., 70%), b. p. 74—76°/0·1 mm., 92—94°/0·4 mm. (Found: C, 73·1; H, 8·5. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%).

o-*Bromobenzyl Phenyl Ether* (*as* VII).—Phenol (19 g.) and then molten *o*-bromobenzyl bromide (50 g.) were added with stirring to the solution from sodium (4·7 g.) and ethanol (50 c.c.), which was then boiled under reflux, concentrated, diluted with water, and extracted with ether. Distillation of the dried extract gave the ether (42 g., 83%), b. p. 187—188°/16 mm., m. p. 40° (Found: C, 58·95; H, 4·5. Calc. for $C_{13}H_{11}OBr$: C, 59·3; H, 4·2%). Huston, Neeley, Fayerweather, D'Arcy, Maxfield, Ballard, and Lewis (*J. Amer. Chem. Soc.*, 1933, **55**, 2146) give m. p. 34—36°.

o-*Phenoxymethylbenzoic Acid* (*as* IV).—A Grignard reagent was prepared by adding a solution of the above ether (30 g.) and ethyl bromide (6 g.) in ether (60 c.c.) to activated magnesium (4·5 g.) under ether (10 c.c.). It was boiled under reflux for 2 hr., cooled, and carboxylated as usual. It yielded the above acid, m. p. 123—124° after crystallisation from light petroleum (b. p. 100—120°), in 7·7 g. (35%) yield. Oppé (*Ber.*, 1913, **46**, 1091) gives m. p. 126°.

o-*Phenoxymethylbenzyl Alcohol* (*as* V).—The above acid, when reduced with lithium aluminium hydride, gave the alcohol, b. p. 222—224°/21 mm., m. p. 49—50°, in 78% yield. Von Braun and Zobel (*Ber.*, 1923, **56**, 2142) give b. p. 216°/15 mm., m. p. 50°.

o-*Phenoxymethylbenzyl Chloride* (*as* I).—A solution of thionyl chloride (2·35 g.) in chloroform (7 c.c.) was added to an ice-cold solution of the above alcohol (4·2 g.) and pyridine (1·55 g.) in chloroform (15 c.c.). The normal treatment then gave the *chloride* (2·7 g., 60%) as an oil, b. p. 206—209°/23 mm., m. p. 38—39·5° after crystallisation from light petroleum (b. p. 40—60°) (Found: C, 72·4; H, 5·8. $C_{14}H_{13}OCl$ requires C, 72·3; H, 5·6%).

o-*Bromobenzyl* tert.-*Butyl Ether* (XVII).—Sodium wire (6 g.) was brought into reaction with a mixture of *tert.*-butanol (16·5 g.) and benzene (100 c.c.) by boiling the stirred mixture under reflux for 15 hr. A solution of *o*-bromobenzyl bromide (XVI) (55 g.) in benzene (100 c.c.) was then added and the boiling continued for 48 hr. Filtration followed by distillation gave the ether (XVII), b. p. 127—128°/16 mm., but analysis showed it was always contaminated with unchanged bromide (XVI), which has b. p. 127—128°/16 mm. When, to avoid this difficulty, an excess of sodium *tert.*-butoxide in the absence of benzene was used, *di-o-bromobenzyl ether*, m. p. 66—67° after recrystallisation from ethanol, was formed as a by-product (Found: C, 47·0; H, 3·3. $C_{14}H_{12}OBr_2$ requires C, 47·2; H, 3·3%).

o-tert.-*Butoxymethylbenzoic Acid* (XVIII).—The Grignard reagent, prepared by the action of a mixture of the ether (XVII) (20 g.) and ethyl bromide on magnesium, when carboxylated as usual gave o-tert.-*butoxymethylbenzoic acid* (10·6 g., 50%), m. p. 86—87° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 69·4; H, 7·9. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

o-tert.-*Butoxymethylbenzyl Alcohol* (XIX).—(*a*) The Grignard reagent prepared from the ether (XVII) but on twice the above scale was treated with paraformaldehyde, and the product, when worked up as usual, gave the alcohol (XIX), b. p. 94—97°/0·2 mm. (10·5 g., 40%), with a fore-run of benzyl *tert.*-butyl ether, b. p. 92—94°/15 mm.

(*b*) The acid (XVIII), when reduced as usual with lithium aluminium hydride, gave the alcohol (XIX), b. p. 160—162°/21 mm., in 58% yield.

The alcohol even when very carefully distilled underwent some decomposition and thus could not be obtained pure (Found: C, 72·6; H, 7·8. Calc. for $C_{12}H_{18}O_2$: C, 74·2; H, 9·2%); incautious heating may cause almost total decomposition with copious evolution of fumes.

o-tert.-*Butoxymethylbenzyl Chloride* (XV).—This *chloride*, prepared in the usual way by the action of thionyl chloride (5 g.) in chloroform (12 c.c.) on the alcohol (XIX) (8·3 g.) and pyridine (3·3 g.) in chloroform (30 c.c.), when cautiously distilled once was obtained as a mobile liquid (5·9 g., 67%), b. p. 69—73°/0·2 mm. (Found: C, 66·8; H, 7·5. $C_{12}H_{17}OCl$ requires C, 67·7; H, 8·0%).

o-2-*Methoxyethylbenzyl Alcohol* (XXI).—The Grignard reagent, prepared by the action of the methyl ether (XX) (13·5 g.) and ethyl bromide (3·4 g.) in ether (50 c.c.) on magnesium (3·6 g.) in the usual way, was treated with paraformaldehyde (2·8 g.) and then boiled under reflux for 16 hr., cooled, and hydrolysed with dilute sulphuric acid. Distillation gave a fore-run of methyl phenethyl ether, b. p. 88—95°/21 mm., followed by the odourless *alcohol* (6·5 g., 62%) (XXI), b. p. 162—166°/23 mm. on refractionation (Found: C, 72·2; H, 8·7. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%).

The above Grignard reagent, when cautiously treated with solid carbon dioxide, gave o-2-*methoxyethylbenzoic acid* (56%), b. p. 131—133°/0·3 mm., m. p. 39—41° after recrystallisation from light petroleum (b. p. 40—60°) (Found: C, 66·7; H, 6·5. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·6%).

o-2-*Methoxyethylbenzyl Chloride* (XXII).—This *chloride*, prepared by the action of thionyl chloride (3·8 g.) in chloroform (10 c.c.) on a mixture of the alcohol (XXI) (5·6 g.) and pyridine

(2·6 g.) in chloroform (25 c.c.), formed an almost odourless mobile liquid (4·4 g., 75%), b. p. 134—136°/17 mm. (Found: C, 65·7; H, 7·4. $C_{10}H_{13}OCl$ requires C, 65·2; H, 7·2%).

p-*Methoxymethylbenzyl Chloride*.—This was prepared from *p*-xylylene dimethyl ether precisely as described for (I), and obtained after fractional distillation as a liquid, b. p. 132—134°/20 mm. Analysis showed that it contained 76% of the chloride.

m-*Xylylene Dimethyl Ether* (XXIII).—*m*-Xylylene dibromide was prepared by Atkinson and Thorpe's method (*J.*, 1907, **91**, 1196). The dibromide (32 g.), when added to a solution obtained from sodium (6·4 g.) and methanol (220 c.c.), gave the *ether* (17·2 g., 86%), an odourless liquid b. p. 128—129°/23 mm. (Found: C, 72·5; H, 8·7. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%).

m-*Bromobenzyl Bromide* (XXV).—*m*-Bromotoluene (41 g.) was maintained at 135—140° whilst bromine (33 g., 11 c.c.) was slowly added without stirring through a tube leading to the bottom of the liquid (cf. Holliman and Mann, *J.*, 1942, 739: Lyon, Mann, and Cookson, *J.*, 1947, 668). Distillation gave the bromide (XXV) (37 g., 74%), b. p. 132—134°/17 mm., which solidified and had m. p. 36—38°. Jackson (*Ber.*, 1876, **9**, 932) gives m. p. 41°.

m-*Bromobenzyl Methyl Ether* (XXVI).—The bromide (XXV) (37 g.) was added to a solution obtained from sodium (3·8 g.) and methanol (120 c.c.), which was then boiled under reflux for 1 hr. When worked up as usual, the *ether* (XXVI) was obtained as a liquid (24·7 g., 82%), b. p. 117—118°/21 mm., having a very pleasant odour (Found: C, 47·7; H, 4·8. C_8H_9OBr requires C, 47·7; H, 4·5%).

m-*Methoxymethylbenzonitrile* (XXIX).—A mixture of the ether (XXVI) (67 g.), cuprous cyanide (30 g.), and dry pyridine (50 c.c.) was heated at 215—225° for 16 hr. Working up as described for (VIII) gave the *nitrile* (37·5 g., 76%), a highly refractive liquid, b. p. 123—126°/11 mm., having a faint benzonitrile-like odour (Found: C, 73·2; H, 6·0; N, 9·6. C_9H_9ON requires C, 73·4; H, 6·1; N, 9·5%).

m-*Methoxymethylbenzoic Acid* (XXVII).—(*a*) The Grignard reagent, prepared by the action of the ether (XXVI) (22 g.) and ethyl bromide (6 g.) in ether (60 c.c.) on magnesium (4·2 g.) under ether (5 c.c.), gave on carboxylation the *acid* (XXVII) (5·1 g., 30%) as a colourless liquid, b. p. 120—126°/0·1 mm., which solidified, and when recrystallised from light petroleum (b. p. 60—80°) had m. p. 63—64° (Found: C, 65·0; H, 6·2. $C_9H_{10}O_3$ requires C, 65·0; H, 6·0%).

(*b*) A mixture of the nitrile (XXIX) (17·5 g.), ethanol (45 c.c.), and 10% aqueous sodium hydroxide (220 c.c.) was boiled under reflux for 2 hr. The acid (XXVII), isolated as usual and recrystallised as before, had m. p. 64—66°, alone and mixed; the yield was 16·4 g. (85%).

m-*Methoxymethylbenzyl Alcohol* (XXVIII).—A solution of the acid (XXVII) (5 g.) in ether (50 c.c.) was reduced with lithium aluminium hydride (1·5 g.) in ether (60 c.c.). The product when worked up gave the alcohol (XXVIII), b. p. 156°/20 mm. (Found: C, 69·7; H, 7·8. Calc. for $C_9H_{12}O_2$: C, 71·0; H, 7·8%) (2·35 g., 51%). Since low carbon values were obtained even after repeated refractionation, the alcohol was converted into the 1-*naphthylurethane*, m. p. 89—90° after recrystallisation from light petroleum (b. p. 80—100°) (Found: N, 4·5. $C_{20}H_{19}O_3N$ requires N, 4·4%).

In view of the high yield of the acid (XXVII) from the nitrile (XXIX), in contrast to the low yield from the Grignard reagent (cf. *a* above), the action of formaldehyde on this reagent to give the alcohol (XXVIII) was not investigated.

m-*Methoxymethylbenzyl Chloride* (XXIV).—(*a*) Addition of thionyl chloride (1·85 g.) in chloroform (5 c.c.) to a solution of the alcohol (XXVIII) (2·35 g.) and pyridine (1·15 g.) in chloroform (12 c.c.), followed by the usual working up, gave the *chloride* (1·9 g., 74%), b. p. 122—124°/13 mm. (Found: C, 63·2; H, 6·3. $C_9H_{11}OCl$ requires C, 63·4; H, 6·4%).

(*b*) The crude chloride (XXIV) was also prepared as described for (I), zinc chloride (*ca.* 0·01 g.) being added to a solution of *m*-xylylene dimethyl ether (XXIII) (8·5 g.) and acetyl chloride (3·5 g.) in carbon tetrachloride (6 c.c.), which became very hot. Distillation of the extract gave a sample of the chloride (6·7 g.), b. p. 126—127°/17 mm., the analysis of which indicated the presence of *ca.* 16% of unchanged ether (Found: C, 64·9; H, 7·4%).

m-*Bromobenzyl Phenyl Ether* (XXX).—This ether, prepared from the bromide (XXV) precisely as the *o*-isomer, was isolated as a liquid, b. p. 198—201°/20 mm., which readily solidified and then had m. p. 36—38° (Found: C, 59·6; H, 4·5. Calc. for $C_{13}H_{11}OBr$: C, 59·2; H, 4·2%). Huston *et al.* (*loc. cit.*) give m. p. 36—37°.

m-*Phenoxymethylbenzyl Alcohol* (XXXI).—The Grignard reagent prepared by the action of the ether (XXX) (32 g.) and ethyl bromide (6·7 g.) in ether (70 c.c.) on magnesium (4·8 g.) under ether (5 c.c.) was treated with paraformaldehyde (5·8 g.), and the mixture was boiled under reflux for 12 hr. Working up as usual gave the *alcohol* (XXXI) as an oil, b. p. 220—228°/18 mm., which solidified on cooling (14·1 g., 54%). Recrystallisation from light petroleum (b. p. 60—

80°) gave leaflets, m. p. 57—58° (Found: C, 78·6; H, 6·7. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). A considerable earlier fraction, b. p. 158—180°/19 mm., was presumably crude benzyl phenyl ether.

m-*Phenoxymethylbenzoic Acid*.—The Grignard reagent, prepared as above, on carboxylation gave this *acid*, m. p. 116—117° after recrystallisation from light petroleum (b. p. 80—100°) (Found: C, 73·3; H, 5·6. $C_{14}H_{12}O_3$ requires C, 73·6; H, 5·3%), in 40% yield.

m-*Phenoxymethylbenzyl Chloride* (XXXII).—This chloride, prepared by the action of thionyl chloride (7·6 g.) in chloroform on a solution of the alcohol (XXXI) (13·9 g.) and pyridine (5·1 g.) in chloroform (45 c.c.), was isolated as an oil (12·7 g., 86%), b. p. 160—161°/0·3 mm., 211—214°/21 mm., which however underwent slight decomposition on fractionation and could not be obtained pure (Found: C, 71·3; H, 5·6. Calc. for $C_{14}H_{13}OCl$: C, 72·3; H, 5·6%). It was converted into the *nitrile*, b. p. 160—162°/0·2 mm., which readily solidified and when recrystallised from light petroleum (b. p. 60—80°) had m. p. 47—48° (Found: C, 80·7; H, 5·5; N, 6·0. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·2%). Hydrolysis with aqueous-ethanolic sodium hydroxide furnished m-*phenoxymethylphenylacetic acid*, leaflets (from ethanol), m. p. 113—114° (Found: C, 74·3; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·3; H, 5·7%), in 80% yield.

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The Action of Magnesium and of Grignard Reagents on Certain Benzyl Ethers. Part I. The Action of Magnesium on o-, m-, *and* p-*Alkoxy- and -Phenoxy-methylbenzyl Chlorides.*

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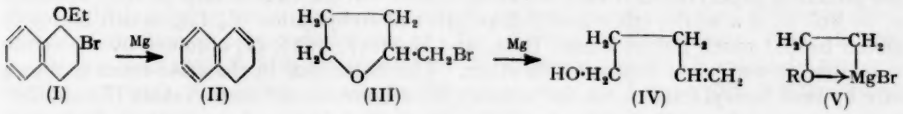
It is shown that although magnesium reacts with the above *meta*-compounds to give normal Grignard reagents, it reacts with the *ortho*- and *para*-compounds to give amorphous polymers of approximate composition $(C_8H_8)_x$. The mechanism of these reactions is discussed, and correlated with that of the interaction of magnesium with other kindred systems.

IT has long been known that sodium and magnesium give an apparently anomalous reaction with 2-alkoxy- and 2-aryloxy-ethyl halides, whereby an olefin and the metallic alkoxide or aryloxide are formed: $RO{\cdot}CH_2{\cdot}CH_2X + 2Na \longrightarrow CH_2{:}CH_2 + NaOR + NaX$. Grignard (*Compt. rend.*, 1904, **138**, 1048) showed that magnesium and 2-phenoxyethyl bromide give ethylene and sodium reacts similarly with the chloride (Wohl and Berthold, *Ber.*, 1910, **43**, 2177). Moreover, the presence of certain substituents in the 1- and 2-positions of the ethane residue does not inhibit this reaction. Thus Wislicenus (*Annalen*, 1878, **192**, 106) showed that 2-chloroacetal, $(EtO)_2CH{\cdot}CH_2Cl$, reacted with sodium to give ethyl vinyl ether and sodium ethoxide and chloride: similarly the ortho-esters of α-halogeno-acids give keten acetals:

$$(EtO)_3C{\cdot}CHBrR + Na \longrightarrow (EtO)_2C{:}CHR + NaOEt + NaBr$$

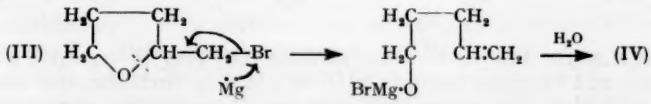
(Walters and McElvain, *J. Amer. Chem. Soc.*, 1940, **62**, 1482). A particularly interesting example is 2-bromo-1-ethoxytetralin (I), which with magnesium furnishes 1 : 2-dihydronaphthalene (II) (von Braun and Kirschbaum, *Ber.*, 1921, **54**, 597): it is clear that in this reaction the compound (I) is acting as a 1 : 2-disubstituted derivative of 2-ethoxyethyl bromide. Paul (*Bull. Soc. chim.*, 1933, **53**, 421) extended the reaction to heterocyclic systems, showing that 2-bromomethyltetrahydrofuran (III) on reaction with magnesium followed by hydrolysis gave pent-4-en-1-ol (IV), and it was subsequently found that (IV) is also produced by the action of sodium on the 2-chloro-derivative (as III) (Gambert, Linstead, and Rydon, *J.*, 1937, 1972). Grignard, Paul, and also Swallen and

Boord (*J. Amer. Chem. Soc.*, 1930, **52**, 651) suggested that the reaction with magnesium involved the formation of a normal but unstable Grignard reagent, which rapidly decomposed: on the other hand, a chelation mechanism, involving intermediates of

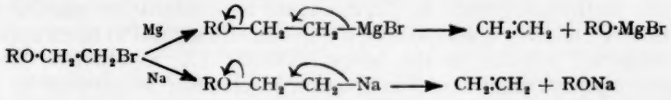


type (V), was put forward by Tallman (*ibid.*, 1934, **56**, 126), who was unable to detect the formation of a Grignard reagent when magnesium reacted with eight 2-alkoxyethyl bromides, in each case with the liberation of ethylene.

Robinson and Smith (*J.*, 1936, 195) confirmed Paul's results and suggested the following mechanism:



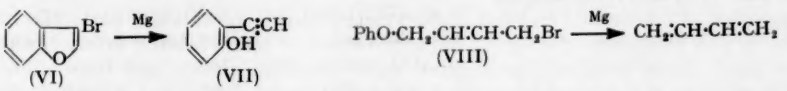
In this scheme the fission of the O–C bond is considered to occur simultaneously with a nucleophilic attack on the bromine by the metal. Since formation of any Grignard reagent presumably involves a similar attack on a halogen atom, it follows that the actual fission of the O–C bond may occur at any time during the attack by the metal or after an actual Grignard reagent has been formed, the ease of the fission being determined by several factors, *e.g.*, the stability of the alkoxide anion which is produced. The mechanism in the simpler ethyl halides may therefore conveniently be indicated:



The fact that sodium usually gives the same ethylene derivative indicates a similar tendency to form a 2-substituted sodium alkyl which then decomposes by the same electronic mechanism: here again, however, the fission of the O–C link may occur almost simultaneously with the reaction of the sodium with the halogen (Crombie and Harper, *J.*, 1950, 1707, 1715).

The general subject has been discussed by Amstutz (*J. Org. Chem.*, 1944, **9**, 30), who also used lithium for this type of reaction, and by Crombie and Harper (*loc. cit.*).

Two extensions follow from the mechanism suggested above. 2-Alkoxy(or 2-aryloxy)-vinyl halides should give acetylenes, whilst vinylogues of the 2-alkoxy(or 2-aryloxy)ethyl halides should give dienes. The first extension has been established by Jacobs, Cramer, and Weiss (*J. Amer. Chem. Soc.*, 1940, **62**, 1849) who showed that 2-phenoxyvinyl bromide and sodium form acetylene and sodium phenoxide, and by Reichstein and Baud (*Helv. Chim. Acta*, 1937, **20**, 892), who showed that 3-bromobenzofuran (VI) on reaction with magnesium, followed by treatment with carbon dioxide and subsequent hydrolysis, gives *o*-hydroxyphenylacetylene (VII) as the main product, and only a very small yield of benzofuran-3-carboxylic acid. Luttringhaus, Saar, and Hauschild (*Ber.*, 1938, **71**, 1673) established the second extension, by showing that 1-bromo-4-phenoxybut-2-ene (VIII)



and magnesium afford butadiene: for other examples see Schubert, Lanka, and Liddicoet (*Science*, 1952, **116**, 124).

It is clear, however, that on the basis of the above mechanism a similar type of reaction

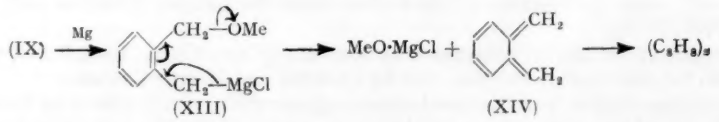
should be given by compounds analogous to the vinylogues (VIII) but in which the ·CH:CH· unit of (VIII) has been replaced by a similarly "electron-conducting" *o*- or *p*-phenylene group. This we find to be the case. *o*-Methoxymethylbenzyl chloride (IX) (see preceding paper) reacts readily with magnesium, but the only definite product obtained on hydrolysis is a white, ether-insoluble polymer of composition $(C_8H_8)_x$, which is closely similar to that which Baker, Banks, Lyon, and Mann (*J.*, 1945, 27) obtained by the action of sodium on *o*-xylylene dibromide in ether. This behaviour in the *ortho*-series is shown only by such benzyl halides, for the homologous *o*-bromobenzyl methyl ether (X) and 2-*o*-methoxymethylphenylethyl chloride (XI) form normal Grignard reagents in high yield (Holliman and Mann, *J.*, 1947, **1634**), and we now find that *o*-2-methoxyethylbenzyl chloride (XII) also does so.

(IX) (X) (XI) (XII)

We suggest that the behaviour of the chloride (IX) may be regarded as due to the initial formation of a Grignard reagent (XIII) in which an electronic drift similar to that discussed above occurs, and causes decomposition to magnesium methoxychloride and *o*-quinodimethane (XIV), which then rapidly polymerises. However, since, as stated above, in this and similar reactions discussed below, rupture of the ether linkage may be almost simultaneous with the initial action of the magnesium, compounds such as (XIII) may have, at the most, a transient existence.

It is noteworthy that the resonance energy of *o*-quinodimethane (XIV) has been calculated by quantum-mechanical means to be of the same order of magnitude as that of a benzene nucleus (Pullman, Berthier, and Pullman, *Bull. Soc. chim.*, 1948, **450**; Namiot, Dyatkina, and Syrkin, *Compt. rend. Acad. Sci. U.R.S.S.*, 1945, **48**, 267) and that the reactivity of the methylene groups in (XIV) should be similarly comparable to that of simple aromatic free radicals; consequently, *o*-quinodimethane (XIV) bears approximately the same "energetic" relation to the benzyl chloride (IX) as ethylene bears to, for example, 2-methoxyethyl chloride. The reaction mechanism we propose by analogy is therefore supported also on these grounds.

The poly-*o*-xylylene formed from *o*-quinodimethane (XIV) softens at *ca.* 60° to a plastic mass which can be drawn out into long threads.



(XIII) (XIV)

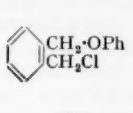
o-Phenoxymethylbenzyl chloride (XV) reacts similarly with magnesium, with the formation of the polymer $(C_8H_8)_x$ and (on the addition of water) the liberation of phenol, in confirmation of the suggested mechanism.

Incidentally, it is known that benzyl ethers are attacked by organo-lithium and -sodium compounds (cf. Wittig and Löhmann, *Annalen*, 1942, **550**, 260) but, with the exception of those types now under investigation, are usually stable to magnesium and Grignard reagents under normal conditions (see preceding paper for examples). In view of this potential complication, we have limited our study to the action of magnesium on the chloride (IX) and its analogues.

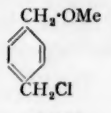
The action of magnesium on *o-tert.*-butoxymethylbenzyl chloride is of particular interest, because in this compound the strong inductive effect of the *tert.*-butyl group towards the oxygen might have reversed the electron drift described above, and thus allowed the chloride to form a Grignard reagent of normal stability. We find, however, that this chloride reacts slowly, but also gives the polymeric *o*-xylylene, and it is clear therefore that this inductive effect is insufficient.

The reaction of *p*-methoxymethylbenzyl chloride (XVI) with magnesium is, as

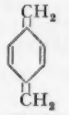
expected, analogous to that of the *o*-isomer (IX). Though sluggish, it affords a white polymer of approximate composition $(C_8H_8)_x$ which, however, unlike its *o*-isomer, does not soften appreciably below 200° and cannot be drawn into threads. This is probably identical with the *lin.*-poly-*p*-xylylene described by Brown and Farthing (*J.*, 1953, 3270). There is little doubt that a similar mechanism applies in this case also, involving intermediate formation of *p*-quinodimethane (XVII). Szwarc (*J. Chem. Phys.*, 1948, **16**, 128; *J. Polymer Sci.*, 1951, **6**, 319) has found that the intermediate (XVII), which he prepared by the pyrolysis of *p*-xylene, is reasonably stable as a gas but rapidly polymerises on



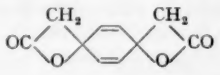
(XV)



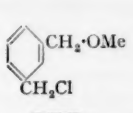
(XVI)



(XVII)



(XVIII)



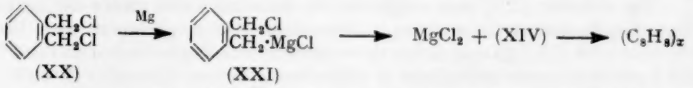
(XIX)

cooling; he also prepared a number of analogues, of comparable reactivity (see also Szwarc, *Discuss. Faraday Soc.*, 1947, **2**, 46; Coulson, Craig, Maccoll, and Pullman, *ibid.*, p. 36). Hagemeyer (U.S.P. 2,4871,742/1949) claimed to have prepared (XVII) by the thermal decomposition of the compound (XVIII) obtained by the addition of keten to *p*-benzoquinone.

A further corollary to the above mechanism is that *m*-methoxymethylbenzyl chloride (XIX) should be unable to show this type of reaction. We find that, although the chloride (XIX) reacts only slowly with magnesium, so that the " entrainment method " has to be employed, a normal Grignard reagent results and when treated with water gives methyl *m*-methylbenzyl ether. *m*-Phenoxymethylbenzyl chloride, however, reacts readily with magnesium alone, and hydrolysis of the Grignard reagent similarly gives *m*-methylbenzyl phenyl ether in high yield. In neither case was any polymer formed.

Now the mechanism proposed involves a potential carbanion such as (XIII), since only then can the methoxyl group be eliminated as the stable methoxide ion. In contrast, therefore, any reagent which when applied to (IX) causes the benzyl group to act as a potential cation must also cause it to show " normal " behaviour. Thus the chloride (IX) when treated with potassium cyanide gives the benzyl cyanide, with sodium iodide gives the benzyl iodide (p. 2820) and with sodiodiphenylphosphine forms *o*-methoxymethylbenzyldiphenylphosphine (see following paper).

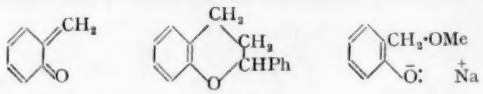
A further example of the formation of the *o*-quinodimethane (XIV) is afforded by *o*-xylylene dichloride (XX), which, unlike the corresponding dibromide (cf. Baker *et al.*, *loc. cit.*), reacts very readily with magnesium with the formation of a white ether-insoluble polymer, apparently identical with that obtained from the chloride (IX). This polymer is the main product under widely varied conditions and, since the mildest conditions used undoubtedly precluded extensive Wurtz-type coupling, it is probable that the dichloride (XX) first forms the mono-Grignard reagent (XXI), which rapidly loses magnesium chloride to form *o*-quinodimethane (XIV), and the usual polymerisation then immediately follows. We failed to confirm Hersch's claim (U.S.P. 2,615,033/1952), based on inadequate evidence, that the dichloride (XX) gives a normal di-Grignard reagent with magnesium.



(XX) (XXI)

There is considerable evidence (Hultzsch, *Ber.*, 1941, **74**, 898; Hultzsch, " Chemie der Phenolharze," Springer, Berlin, 1st Edn., 1950, p. 63) that the highly reactive and readily polymerised *o*-quinomonomethane (XXII) and its derivatives are intermediates in the formation of phenol–formaldehyde resins, and in the self-condensations of *o*-phenolic alcohols generally. Hultzsch (*J. prakt. Chem.*, 1941, **158**, 275) also claims that the synthesis of many chromans and chromens by the condensation of saligenins with ethylenes and acetylenes—for example, condensation of saligenin with styrene to 2-phenylchroman (XXIII)—proceeds by " diene " addition of the ethylene or acetylene to the

intermediate (XXII) derived from the saligenin. Further, *o*-methoxymethylphenol readily decomposes (Thiele and Dimroth, *Annalen*, 1899, **305**, 110), particularly in the presence of bases, to form a resinous polymer with liberation of methanol. This can be explained by a mechanism analogous to that suggested for (IX) but involving the intermediate (XXII); the sodium salt (XXIV) of the phenol can eliminate a methoxide ion, leaving (XXII) which immediately polymerises; the sodium methoxide formed repeats the decomposition, which when once started proceeds to completion.



(XXII) (XXIII) (XXIV)

We are now investigating the application of the considerations discussed above to systems containing *o*-quinomonomethane-imines, *i.e.*, the nitrogen analogues of (XXII).

Experimental

The magnesium used throughout had been activated by Holliman and Mann's method (*J.*, 1942, 739), metallic turnings being used instead of powder.

o-*Methoxymethylbenzyl Chloride* (IX) *and Magnesium.*—A solution of the chloride (7 g.) in ether (35 c.c.) was added dropwise to magnesium (1·1 g.) under ether (5 c.c.). A gentle reaction proceeded smoothly, with deposition of an amorphous white solid. The mixture was then boiled under reflux for 3 hr., cooled, and then stirred while hydrolysed by the addition of aqueous ammonium chloride. Filtration gave the crude ether-insoluble polymer (2·4 g.).

The ether solution, when dried and distilled, gave fractions, (*a*) b. p. <130°/0·1 mm. (1 g.), mainly unchanged chloride (IX), (*b*) b. p. 130—170°/0·1 mm., a pale yellow ethanol-soluble oil (0·6 g.), and (*c*) b. p. 170—245°/0·1 mm., a viscous brown syrup (0·5 g.) sparingly soluble in ethanol.

The polymer was partially purified by dissolution in benzene followed by precipitation with ethanol, but traces of magnesium derivatives and of organic solvents were difficult to remove in this and in all other samples of amorphous polymeric material [Found: C, 91·3; H, 7·7. Calc. for $(C_8H_8)_x$: C, 92·3; H, 7·7%]: it softened at *ca.* 60° to form a plastic mass.

When set aside, fraction (*b*) remained as a mobile oil: (*c*) formed a gum which could not be obtained crystalline and appeared also to be polymeric.

When the reaction with magnesium was carried out as above, and the cooled product treated with a large excess of solid carbon dioxide, subsequent hydrolysis furnished only the ether-insoluble polymer with a smaller quantity of the ether-soluble gum.

o-*Phenoxymethylbenzyl Chloride* (XV) *and Magnesium.*—A solution of the chloride (1 g.) in ether (5 c.c.) was similarly added to magnesium (0·12 g.) under ether (0·5 c.c.), a white solid separating as before. The mixture was then boiled under reflux for 3 hr., cooled and hydrolysed as before. The white ether-insoluble polymer (0·5 g.) softened at *ca.* 60°, and was apparently identical with that similarly obtained from (IX). The aqueous layer was repeatedly extracted with ether, and the extracts were combined and then extracted with 10% aqueous sodium hydroxide. The alkaline extract, when acidified and extracted with ether, gave phenol, identified by (*a*) a purple coloration with ferric chloride and (*b*) conversion by bromine water into *s*-tribromophenol, m. p. 92—93° alone and mixed [0·65 g., indicating 50% yield of phenol from (XV)]. The chloride (XV) was unaffected by bromine water under similar conditions.

o-tert.-*Butoxymethylbenzyl Chloride and Magnesium.*—An experiment with these reagents carried out as that with (IX), gave a rather slow reaction with deposition of an insoluble product. Heating and hydrolysis gave ultimately a colourless polymer (Found: C, 89·9; H, 7·7%), softening at *ca.* 60°, almost certainly identical with that obtained from (IX). No indication of the formation of a normal Grignard reagent could be obtained.

o-2-*Methoxyethylbenzyl Chloride* (XII) *and Magnesium.*—When a solution of the chloride (4·4 g.) and ethyl bromide (1·3 g.) in ether (35 c.c.) was added to magnesium (0·9 g.) under ether (5 c.c.), a reaction ensued with the formation of a white precipitate which subsequently redissolved. The dark solution was heated, then cooled, and hydrolysed with dilute hydrochloric acid, no insoluble products being obtained. Distillation of the ether layer gave (*a*) *methyl* 2-o-*methylphenylethyl ether*, b. p. 112—118°/32 mm., 204—206°/760 mm., a liquid having a pleasant odour (Found: C, 79·1; H, 9·4. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%), and

(*b*) a fraction, b. p. 220—230°/20 mm., too small for purification, which was almost certainly *oo'*-di-(2-methoxyethyl)dibenzyl [cf. reaction of (XIX) with magnesium].

p-*Methoxymethylbenzyl Chloride* (XVI) *and Magnesium.*—This chloride reacted with magnesium much less readily than did (IX), and it was therefore mixed with ethyl bromide to accelerate the reaction. A solution of the chloride (XVI) (6·7 g.) and ethyl bromide (2 g.) in ether (50 c.c.) was added dropwise to activated magnesium (1·5 g.) under ether (2 c.c.). Reaction occurred slowly with deposition of a white amorphous solid. The mixture was then heated, hydrolysed, and filtered as described for (IX). The amorphous solid (3·3 g.), after thorough washing and drying, had no definite m. p. and did not soften below 250° : it was insoluble in ethanol and almost so in benzene, and consequently all samples after various attempted purifications retained a magnesium residue (Found : C, 86·6; H, 7·9%).

m-*Methoxymethylbenzyl Chloride* (XIX) *and Magnesium.*—When a solution of the chloride (6·7 g.) and ethyl bromide (2·1 g.) in ether (50 c.c.) was added to magnesium (1·5 g.) under ether (2 c.c.), a very sluggish reaction ensued with deposition of a gum. The mixture was boiled for 3 hr., then cooled and hydrolysed with dilute sulphuric acid, the gum redissolving. Fractionation of the dried ether layer gave the fractions (*a*), b. p. 108—120°/42 mm., a colourless liquid of very pleasant odour, and (*b*) b. p. 226—230°/18 mm., a colourless oil Fraction (*a*) could not be purified by fractional distillation and was identified as methyl *m*-methylbenzyl ether, by selective oxidation with cold dilute aqueous potassium permanganate to *m*-toluic acid, m. p. 106—107° (alone and mixed). Fraction (*b*) was crude 3 : 3'-di(methoxymethyl)dibenzyl : since distillation on this small scale did not give a pure sample (Found : C, 78·3; H, 8·6. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·1%), it was identified by heating with a mixture (1 : 1 by vol.) of 48% aqueous hydrobromic acid and acetic acid, whereby it furnished 3 : 3'-*di(bromomethyl)dibenzyl*, colourless crystals, m. p. 80—81°, from ethanol (Found : C, 52·4; H, 4·6. $C_{16}H_{16}Br_2$ requires C, 52·2; H, 4·3%). The formation of this dibenzyl derivative was not unexpected, as benzyl halides when treated with magnesium under vigorous conditions frequently give such derivatives.

m-*Phenoxymethylbenzyl Chloride and Magnesium.*—A solution of the chloride (5 g.) in ether (15 c.c.) was added dropwise to magnesium (0·6 g.) under ether (5 c.c.) : reaction proceeded readily with formation of a brown solution which was then boiled for 0·5 hr., cooled, and hydrolysed with aqueous ammonium chloride. The aqueous layer was extracted repeatedly with ether, and the united ether extracts were extracted with dilute aqueous sodium hydroxide. The ether on distillation gave m-*methylbenzyl phenyl ether*, b. p. 168—170°/17 mm. (Found : C, 85·0; H, 7·1. $C_{14}H_{14}O$ requires C, 84·9; H, 7·0%) (2·65 g., 62%).

The alkaline extract, when acidified and extracted with ether, furnished phenol, identified and estimated as *s*-tribromophenol, m. p. 88—90° (alone and mixed) (0·2 g., corresponding to *ca.* 2% yield from the chloride).

o-*Xylylene Dichloride* (XX) *and Magnesium.*—(i) A solution of the dichloride (0·25 g.) in ether (5 c.c.) was added dropwise to magnesium (0·1 g.) under ether (2 c.c.), a reaction occurring steadily with deposition of a white solid. Hydrolysis with aqueous ammonium chloride followed by filtration gave an amorphous white polymer, which softened at *ca.* 60° (Found : C, 88·9; H, 7·7%). Evaporation of the ethereal layer gave a gum which was very soluble in benzene, from which it was precipitated as a gum by addition of ethanol, in which it was very sparingly soluble.

(ii) The above experiment was repeated on a larger scale with unactivated magnesium, the deposition of the white solid again occurring. The mixture was then added to an excess of solid carbon dioxide and allowed slowly to evaporate. No acid could be detected in the residue, which contained the above two polymers.

(iii) In order to detect the presence of even a smaller proportion of a true di-Grignard reagent, the addition of phenyldichlorophosphine, which would have formed phenyl*iso*phosphindoline (see following paper), was employed. A solution of the dichloride (XX) (5 g.) in ether (30 c.c.) was therefore slowly added to magnesium (1·5 g.) under ether (10 c.c.) with the usual deposition of white solid as in (i), and the complete mixture then boiled under reflux for 2 hr., cooled, treated with a solution of phenyldichlorophosphine (5 g.) in benzene (10 c.c.), and again boiled for 2 hr. After cooling and hydrolysis, the ether-insoluble polymer, as in (i), was collected. Distillation of the ethereal layer gave only unchanged dichlorophosphine (0·1 g.), and a polymeric residue which on cooling formed a stone-hard mass.

(iv) Experiment (iii) was repeated, with the mixture however cooled in ice-water throughout, the dichlorophosphine being added in ether (35 c.c.) instead of benzene. Again only polymeric products were obtained, without even the odour of a tertiary phosphine.

(v) The dichloride (XX) and the dichlorophosphine were added simultaneously to the cold magnesium, in the hope that the mono-Grignard reagent (XXI) on formation would now immediately react with the chlorophosphine and thus decomposition to (XIV) would be arrested: further reaction with magnesium, with subsequent cyclisation, might then ensue. However formation of the polymer was still the dominant reaction. A solution of the dichloride (XX) (8·75 g.) and phenyl dichlorophosphine (8·95 g., 1 mol.) in ether (30 c.c.) was added dropwise to magnesium (2·7 g., 2·2 atoms) in ether (5 c.c.) under nitrogen, and the mixture then stirred for 5 hr. After hydrolysis with aqueous ammonium chloride, and drying, the ethereal layer yielded only unchanged dichloride (XX), m. p. 54—55° (alone and mixed). Filtration gave a considerable yield of the polymer, soluble in benzene but reprecipitated by ether, and indistinguishable from that obtained in (i)—(iv) above. We are indebted to Dr. I. T. Millar for this experiment.

A Rouse Ball Research Studentship, awarded by Trinity College, is gratefully acknowledged (F. H. C. S.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 25th,* 1954.]

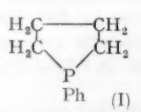
The Preparation and Properties of 2-*Phenyl*isophosphindoline. *A New Class of Co-ordinated Metallic Compounds.*

By FREDERICK G. MANN, IAN T. MILLAR, and FREDERICK H. C. STEWART.

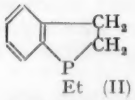
[Reprint Order No. 5241.]

Two syntheses are described which furnish respectively the above *iso*-phosphindoline and its quaternary salts. 2-Phenyl*iso*phosphindoline has many of the normal properties of a tertiary phosphine but is unique in that with palladium dichloride and dibromide it gives crystalline derivatives of composition $[(C_{14}H_{13}P)_2PdCl]$ and $[(C_{14}H_{13}P)_2PdBr]$ respectively. These compounds associate in solution but otherwise are stable derivatives of univalent palladium, and represent an entirely novel class of complex metallic compound.

ONLY two types of compound having a ring-system consisting of four carbon atoms and one phosphorus atom have hitherto been recorded, namely, 1-phenyltetramethylenephosphine (I) (Grüttner and Krause, *Ber.*, 1916, **49**, 438) and 1-ethylphosphindoline (II) (Mann and Millar, *J.*, 1951, 2205). We have now investigated the synthesis of 2-phenyl*iso*phosphindoline (III).



(I)



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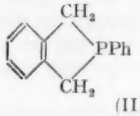

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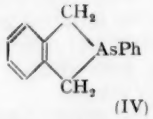


(IV)

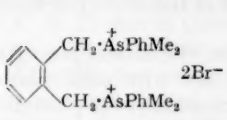
The arsenic analogue of (III), *i.e.*, 2-phenyl*iso*arsindoline (IV), can be prepared by the interaction of *o*-xylylene dibromide, phenyldichloroarsine, and sodium, the reaction being catalysed by ethyl acetate (Lyon and Mann, *J.*, 1945, 30). A similar experiment, using phenyldichlorophosphine, yielded however only a trace of the crude *iso*phosphindoline (III); this result was not unexpected, as Holliman and Mann (*J.*, 1943, 547) have shown that, although *o*-2-bromoethylbenzyl bromide, $C_6H_4(CH_2Br)\cdot C_2H_4Br$, condenses with phenyldichloroarsine and sodium to give 2-phenyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline in good yield, with phenyldichlorophosphine under similar conditions it gives only a minute yield of the tetrahydro*iso*phosphinoline.

2-Phenyl*iso*arsindoline (IV) is, however, most readily prepared by the interaction of *o*-xylylene dibromide and phenyldimethylarsine to give a crude product which contains the diquaternary bromide (V) as the main component and on thermal decomposition gives the arsine (IV) in 57% yield (Lyon, Mann, and Cookson, *J.*, 1947, 662). Experiments, for which we are greatly indebted to Dr. Joan A. Reid, indicate that similar diquaternary salts

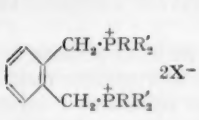
(VI) are formed by the interaction of the dibromide with phenyldimethyl- and phenyldiethyl-phosphine, but these salts when heated in a vacuum gave no detectable 2-substituted *iso*phosphindolines.

o-Xylylene dibromide in ether–benzene reacted readily with phenylphosphinebis(magnesium bromide), $Ph{\cdot}P(MgBr)_2$, but the organic product consisted almost exclusively of an amorphous insoluble powder, apparently produced by extensive linear condensation of the dibromide with the magnesium derivative. However this amorphous material decomposed when heated in a vacuum, with the production of the crude *iso*phosphindoline in 4% yield: redistillation gave the pure phenyl*iso*phosphindoline as a colourless liquid which has an unpleasant odour and readily undergoes oxidation on exposure to the air.

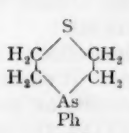
The formation of amorphous products in this type of reaction is not novel. Job, Reich, and Vergnaud (*Bull. Soc. chim.*, 1924, **35**, 1404) showed that phenylarsinebis(magnesium bromide), $Ph{\cdot}As(MgBr)_2$, and 2 : 2′-dichlorodiethyl sulphide formed a resinous material from which tetrahydro-4-phenylthiarsine (VII) could be extracted in only 7% yield. Beeby and Mann (*J.*, 1951, 886) found that this Grignard reagent reacted similarly with 2 : 2′-dibromodiethyl ether to give an insoluble product which on strong heating decomposed to tetrahydro-4-phenyloxarsine (as VII), and reacted with *NN*-bis-2-bromoethylaniline to give a resinous material and the crystalline hexahydro-1 : 4-diphenyl-1 : 4-azarsine (VIII). In all these cases, the production of insoluble amorphous products is probably the result of extensive—and presumably linear—condensation.



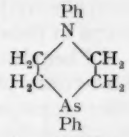
(V)



(VI)



(VII)

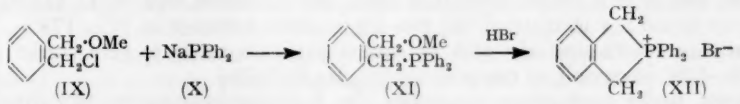


(VIII)

In view of the low yield of the *iso*phosphindoline (III) by the above method, other synthetic routes were investigated, particularly those which would avoid the use of the unpleasant phenylphosphine. Interaction of ethereal *o*-xylylene dichloride and magnesium in the presence, or with the subsequent addition, of phenyldichlorophosphine gave solely the polymeric *o*-xylylene, $(C_8H_8)_x$ (see previous paper). A mixture of the dichloride and the dichlorophosphine in boiling di-*n*-butyl ether, when treated with zinc, gave the same product.

It has been shown by Mann and Smith (*J.*, 1952, 4544) that when phenylarsine in liquid ammonia solution is treated in turn with two equivalents of sodium and of ethyl bromide, a good yield of phenyldiethylarsine results. In a model experiment, phenylarsine was similarly treated with two equivalents of sodium and one of *o*-xylylene dibromide, but no phenyl*iso*arsindoline (IV) was formed and only arsenobenzene, PhAs:AsPh, could be isolated. In view of this result, parallel experiments with phenylphosphine and the dibromide or dichloride were not undertaken.

It is possibly significant however that, although Mann and Smith (*loc. cit.*) found that simple alkyl groups could thus be introduced into phenylarsine, no cyclic derivatives could be similarly obtained by using ethylene dibromide or trimethylene dibromide, arsenobenzene being formed in each case. In view of this difficulty, in another model experiment diphenylphosphine and sodium, each in liquid ammonia solution, were mixed, and the



(IX) (X) (XI) (XII)

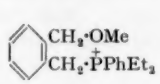
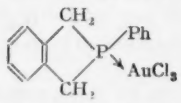
resultant diphenylsodiophosphine (X) then treated with *o*-methoxymethylbenzyl chloride (IX) (cf. pp. 2819, 2829), with the formation of *o*-methoxymethylbenzyldiphenylphosphine (XI), a viscous oil characterised as its crystalline methiodide. This phosphine, when treated in boiling aqueous acetic acid with a stream of hydrogen bromide, underwent conversion into the *o*-bromomethyl derivative, which at once cyclised to 2 : 2-diphenyl*iso*-

phosphindolinium bromide (XII), which in turn was characterised as its highly crystalline picrate.

This synthesis has the advantage that the yields were good even on the small scale on which we were working, and would probably be excellent on a larger scale. On the other hand, it is highly improbable that a diphenylphosphonium salt such as (XII) could be converted into the tertiary 2-phenyl*iso*phosphindoline (III) by thermal decomposition. Such a conversion undoubtedly could be achieved by the use of the sodium derivative of a suitable alkylarylphosphine such as ethylphenylphosphine in place of (X). There is at present however no satisfactory method for the preparation of pure alkylarylphosphines, and no authentic examples of such compounds have been recorded. We have attempted to convert phenyldichlorophosphine by the action of diethylcadmium into phenylethylchlorophosphine, EtPhPCl, but the separation of this chloride from unchanged dichloride, or from phenyldiethylphosphine, proved very difficult, and the reduction of the crude chloride to the phosphine, EtPhPH, by the method employed for diphenylphosphine (Mann and Millar, *J.*, 1952, 3039) completely failed.

A brief examination was made of a possible alternative use of the chloride (IX), which was combined with phenyldiethylphosphine to give diethyl-*o*-methoxymethylbenzylphenylphosphonium chloride (XIII; X = Cl). There was a remote chance that this salt on thermal decomposition might lose ethylene and hydrogen chloride to form the ethylphenyl analogue of the phosphine (XI): actually, this decomposition regenerated the phenyldiethylphosphine, a result which was not unexpected in view of the lability of benzyl groups in phosphonium salts.

2-Phenyl*iso*phosphindoline (III) has, with one striking exception, the normal properties of a tertiary phosphine. It readily gives a crystalline methiodide, and with auric chloride under appropriate conditions gives the colourless crystalline monochloro-(2-phenyl*iso*phosphindoline)gold (XIV), the molecular weight of which shows that the phosphine has the simple " monomeric " structure (III). The stability of the ring system in the tertiary phosphine is shown by the fact that the quaternary methiodide, when heated to *ca.* 250°, decomposes to a mixture of the phosphine (III) and its hydriodide: simple quaternary phosphonium halides which contain both a benzyl and a methyl group, on the other hand,

(XIII)  X⁻  (XIV)

tend on heating to lose the benzyl rather than the methyl group (cf. Meisenheimer, Casper, Höring, Lauter, Lichtenstadt, and Samuel, *Annalen*, 1926, **449**, 213).

The remarkable feature in the chemistry of 2-phenyl*iso*phosphindoline is its reaction with palladous halides. Tertiary phosphines normally react with potassium palladochloride to give, according to the proportions used, either the simple compounds $[(R_3P)_2PdCl_2]$ which are usually bright yellow, or the " bridged " $[(R_3P)_2(PdCl_2)_2]$ which are orange; the bromo-analogues are usually orange and reddish-brown respectively (Mann and Purdie, *J.*, 1935, 1549; 1936, 873). The addition of a hot aqueous-ethanolic solution of potassium palladochloride to a slight excess of the *iso*phosphindoline (III) gives, however, colourless crystals of composition $[(C_{14}H_{13}P)_2PdCl]$, which melt at 177—178° to a clear scarlet liquid. This compound, monochlorobis-(2-phenyl*iso*phosphindoline)palladium, is dimorphic, and gives a second crystalline form, also colourless, melting at 129—131° also to a scarlet liquid: a mixture of the two forms melts however at 177—178°. The *iso*phosphindoline reacts similarly with potassium palladobromide to give scarlet crystals, m. p. 196—198° (decomp.), of composition $[(C_{14}H_{13}P)_2PdBr]$.

However, under appropriate conditions, the *iso*phosphindoline reacts normally with potassium palladochloride to form dichlorobis-(2-phenyl*iso*phosphindoline)palladium, $[(C_{14}H_{13}P)_2PdCl_2]$, yellow crystals, m. p. 256—260° (decomp. with severe darkening), which, unlike the monochloro-derivative, are almost insoluble in boiling ethanol and acetone. The crimson di-iodo-analogue, $[(C_{14}H_{13}P)_2PdI_2]$, has also been isolated.

It is significant that the colourless crystals of the monochloro-compound, when heated

at 60°/0·1 mm. for 2 hours, become pale yellow but on cooling slowly lose this colour. Moreover, solutions of these crystals in warm ethanol, aqueous ethanol, or acetone are bright yellow and on boiling become bright red : on cooling these changes are reversed and (at suitable concentrations) the colourless compound crystallises again. This deepening in colour in solution with increasing temperature (a process which apparently goes to completion when the crystals are melted) would normally be indicative of dissociation : in fact, however, molecular-weight determinations in boiling ethanol and acetone agree closely with six-fold association, *i.e.*, with a formula $[(C_{14}H_{13}P)_2PdCl]_6$.

The red colour of a warm ethanolic solution of the monobromo-compound similarly becomes deep red as the solution is more strongly heated, this change reversing as the solution cools. The molecular weight of the monobromo-compound in solution has not yet been determined, however, owing to insufficient material.

This chloride and bromide are thus apparently co-ordinated derivatives of univalent palladium possessing considerable stability (apart from the factor of physical association) and they represent an entirely new type of co-ordinated metallic compound, of particular interest because authentic and stable derivatives of univalent palladium have not previously been isolated (cf. Sidgwick, "Chemical Elements and their Compounds," Oxford Univ. Press, 1950, p. 1557). Their complete structure cannot be investigated until we have larger supplies. It may be noted, however, that the univalent palladium atom in the simple unit $[(C_{14}H_{13}P)_2PdCl]$ should have an unshared electron, and unless association produces a structure in which this electron becomes shared, the compound should be paramagnetic. Dr. C. M. French of Queen Mary College in a preliminary investigation finds however that the chloride has a diamagnetic susceptibility of *ca.* $-0{\cdot}1 \times 10^{-5}$.

Although the complex palladous halide derivatives of numerous tertiary phosphines have been investigated in the past, 2-phenyl*iso*phosphindoline is the only one known to give these abnormal derivatives, and the very interesting point arises as to what is the particular factor in the structure of this phosphine which determines this behaviour. It is clear that, in the formation of these two compounds, the palladium dichloride and dibromide must undergo reduction to the monohalide which is immediately stabilised by co-ordination with the phosphine, although whether co-ordination precedes or follows reduction is not at present known. This type of reaction is however normal for tertiary phosphines treated in aqueous ethanol with potassium chloroaurate : a transient orange or brown auric compound may separate, but when the solution is warmed reduction and complete decolorisation occur and the aurous chloride is stabilised by formation of the compound $[R_3P\rightarrow AuCl]$. Some of these compounds are so stable that they can be distilled unchanged in a vacuum (Mann, Wells, and Purdie, *J.*, 1937, 1828). It is remarkable that, although the *iso*phosphindoline (III) shows this " normal " behaviour with auric chloride, it is the only known tertiary phosphine which will similarly reduce palladium dihalides to the monohalides under the mild conditions usually employed for these preparations.

We have sought other compounds having structural similarity to the phosphine (III)—and more accessible—to determine whether they also show this behaviour with palladous dihalides. 1-Ethylphosphindoline gives a normal palladous dibromide compound $[(C_{10}H_{13}P)_2PdBr_2]$ (Mann and Millar, *J.*, 1951, 2205), and 1-ethyltetrahydrophosphinoline and 2-ethyltetrahydro*iso*phosphinoline do likewise (Beeby and Mann, *J.*, 1951, 411); we now find that 2-phenyl*iso*arsindoline (IV) similarly gives the yellowish-orange crystalline derivative $[(C_{14}H_{13}As)_2PdBr_2]$.

We have also investigated dibenzylphenylphosphine, which bears a marked structural resemblance to the phosphine (III). Pure dibenzylphenylphosphine has not hitherto been recorded. Michaelis and Gleichmann (*Ber.*, 1882, **15**, 1961) attempted to prepare it by the interaction of benzyl chloride, phenyldichlorophosphine, and zinc, and obtained colourless crystals, m. p. 169—170°, which would not combine with alkyl iodides : it was in fact the phosphine oxide. Meisenheimer *et al.* (*loc. cit.*) and Kamai (*J. Gen. Chem. Russia*, 1932, **2**, 524) prepared the phosphine by the thermal decomposition of benzyldiethylphenylphosphonium chloride, and the former workers also by the interaction of benzylmagnesium chloride and phenyldichlorophosphine; Kamai described the phosphine as a liquid, b. p. >170°/10 mm., but all these workers characterised it solely as derivatives. We find that

the phosphine is very readily oxidised even in solution, but, when prepared by Meisenheimer's second method in an atmosphere of nitrogen, and purified by distillation in a vacuum, it very readily forms colourless crystals, m. p. 71—72°. Treatment of this phosphine with potassium pallado-chloride and -bromide readily gave however the "normal" compounds of composition $[(C_{20}H_{19}P)_2PdCl_2]$ and $[(C_{20}H_{19}P)_2PdBr_2]$ respectively.

Apart from metallic derivatives, it is of interest to compare the properties of 2-phenyl-*iso*indoline, 2-phenyl*iso*phosphindoline (III), and 2-phenyl*iso*arsindoline (IV) and their

	$C_{14}H_{13}N$	$C_{14}H_{13}P$ (III)	$C_{14}H_{13}As$ (IV)
"Base"	M. p. 170°	B. p. 110—112°/0·2 mm.	B. p. 136—138°/0·3 mm.
Methiodide	,, 177	M. p. 207—209°	M. p. 189—191°
Methopicrate	,, 140	,, 88—90	,, 122—123

derivatives. The Table is noteworthy for the almost complete lack of regularity, but the fact that the amine is a solid of reasonably high m. p., whilst the phosphine and arsine are liquid, is particularly striking. Scholtz (*Ber.*, 1898, **31**, 414, 628) prepared the amine by the interaction of *o*-xylylene dibromide and aniline in ethanol or chloroform solution, but did not determine its molecular weight, which however we now find to be normal. To form the methiodide, the amine requires heating with methanolic methyl iodide at 100° for several hours: the phosphine and arsine however readily combine with methyl iodide.

We are now further investigating the above and other syntheses of the *iso*phosphindoline (III), and the reactions of such phosphines with the halides of palladium and of various other metals.

Experimental

2-Phenylisophosphindoline (III).—This preparation was performed in a flask fitted with a sealed stirrer, reflux condenser, and dropping-funnel, and through which nitrogen was passed throughout the experiment. A stirred solution of phenylmagnesium bromide, prepared by the action of bromobenzene (55·3 g., 2·2 mols.) on magnesium (8·94 g., 2·3 atoms) under ether (270 c.c.), was cooled in ice-water whilst phenylphosphine (17·6 g.) in benzene (100 c.c.) was added during 15 min. The mixture was boiled under reflux for 2·5 hr., then cooled again whilst *o*-xylylene dibromide (38·0 g., 0·9 mol.) in benzene (100 c.c.) was added during 30 min., much solid material meanwhile separating. The complete mixture was again boiled for 2·5 hr., cooled, and hydrolysed by the addition of ammonium chloride (17·5 g.) dissolved in air-free chilled water (200 c.c.). The aqueous layer was then siphoned off under reduced pressure.

The organic layer contained much suspended solid, which was collected, washed with benzene and water, and dried under nitrogen.

The combined organic extracts, when dried and evaporated, gave a syrupy amber residue (15 g.), which on distillation in nitrogen at 0·1 mm. gave the fractions: (*a*) b. p. 110—130° (mainly *o*-xylylene dibromide); (*b*) b. p. 130—185° [a mixture of the dibromide and the phosphine (III) identified as the methiodide, m. p. 202—204° (alone and mixed with authentic sample described below)]; and (*c*) b. p. 185—210° (a syrup which did not crystallise or form a crystalline derivative).

The above solid product when dried formed an ivory-coloured translucent glass (30 g.), soluble in ethanol but insoluble in water, benzene, or ether. A portion (25 g.) was powdered and then heated with a "brush" flame in a distillation apparatus in a stream of nitrogen at 0·3 mm. The powder at first decrepitated vigorously, then partly fused, and finally decomposed with darkening as the temperature approached a low red heat; meanwhile a mobile distillate (2·5 g.) collected, followed ultimately by a viscous syrup (*ca.* 1 g.). A considerable dark friable residue was formed.

The distillate on redistillation at 0·2 mm. gave the colourless fractions: (i) b. p. 80—110°, 0·7 g.; (ii) b. p. 110—112°, 0·3 g.; (iii) b. p. 112—130°, 0·4 g.; and an amber residue. Fraction (ii) was pure *2-phenylisophosphindoline* (III) (Found: C, 79·4; H, 6·2. $C_{14}H_{13}P$ requires C, 79·2; H, 6·2%); fractions (i) and (iii) were crude samples pure enough for the preparation of certain derivatives.

It is noteworthy that in the above experiment using *o*-xylylene dibromide (0·9 mol.) a small proportion of this dibromide remained unchanged; when however 0·8 mol. of the dibromide was used, no unchanged dibromide could subsequently be detected, but the final reaction mixture

contained some unchanged di-Grignard reagent, which evolved phenylphosphine during the hydrolysis.

The phosphine possesses a powerful odour resembling that of phenyldiethylphosphine: its ethanolic solution rapidly becomes turbid on exposure to air. The phosphine readily gave a *methiodide* (*i.e.*, *2-methyl-2-phenylisophosphindolinium iodide*), colourless crystals (from ethanol), m. p. 207—209° (decomp.) (Found: C, 50·8; H, 4·3. $C_{15}H_{16}IP$ requires C, 50·85; H, 4·55%): this gave a *methopicrate*, yellow crystals, m. p. 88—90°, from ethanol (Found: C, 55·65; H, 4·4; N, 9·5. $C_{21}H_{18}O_7N_3P$ requires C, 55·4; H, 4·0; N, 9·25%). The pure methiodide, when heated in nitrogen at 20 mm. decomposed above 250°, giving a dark residue and (in small yield) a viscous distillate consisting of the phosphine (III) and its hydriodide. This distillate when basified gave a mobile oil which, when extracted with ether and treated with methyl iodide, re-formed the above methiodide, m. p. 194—198° (decomp.) (alone and mixed) when once recrystallised from ethanol.

The addition of a small excess of the phosphine in ethanol to a warm aqueous solution of chloroauric acid deposited initially a yellow solid, which redissolved when the solution was boiled: heavy colourless crystals of *monochloro-(2-phenylisophosphindoline)gold* (XIV) then separated, m. p. 193° after recrystallisation from ethanol (Found: C, 38·0; H, 3·1%; *M*, ebullioscopic in 0·974% acetone solution, 441. $C_{14}H_{13}ClPAu$ requires C, 37·8; H, 2·95%; *M*, 445).

o-*Xylylene Dibromide and Phenyldichlorophosphine.*—Fine sodium wire (36·8 g., 8 atom-equivs.) was added to a solution of the dibromide (52·8 g.) and the chlorophosphine (35·8 g., 1 mol.) in ether (500 c.c.), which was then boiled under reflux in nitrogen for 11 hr., ethyl acetate (5, 2·5, 2·5 c.c.) being added after 0·5, 3, and 7 hours' boiling. The solution was then filtered through sintered glass under nitrogen pressure and evaporated and the residue distilled at 0·2 mm., giving the fractions: (*a*) b. p. 60—108° (2·5 g.), mainly unchanged dichlorophosphine; (*b*) b. p. 108—134° (2 g.), a colourless liquid; (*c*) b. p. 134—170° (3·5 g.), a pale amber oil; and (*d*) a dark residue (0·5 g.) which did not boil <360°/0·2 mm. and could not be crystallised.

Fraction (*b*) on redistillation gave several indefinite fractions, none of which gave a methiodide. Fraction (*c*), redistilled at 0·5 mm., gave the fractions: (i) b. p. <98° (0·2 g.); (ii) b. p. 98—102° (0·3 g.); (iii) b. p. 118—124°(0·2 g.); (iv) b. p. 130—150° (0·3 g.). Fraction (iii) consisted of the crude phosphindoline (III) (yield, 0·5%), for it readily gave the methiodide, which, once recrystallised from ethanol, had m. p. 190—195° (decomp.), mixed m. p. 200—205° (decomp.).

The solid material in the original ethereal mixture consisted almost entirely of unchanged sodium and its chloride and bromide.

o-*Xylylene Dibromide and Tertiary Phosphines.*—(*a*) A benzene solution of the dibromide and of phenyldimethylphosphine (1 mol.) was boiled under reflux for 2 hr., and the benzene then evaporated under reduced pressure. The glassy residue did not recrystallise. A portion was extracted with cold water, and the extract, after filtration to remove residual unchanged dibromide, was treated with aqueous sodium picrate. The precipitated o-*xylylenebis(phenyldimethylphosphonium) dipicrate* (VI; R = Ph, R′ = Me, X = $C_6H_2O_7N_3$), when thoroughly washed with water and recrystallised from ethanol containing a trace of acetone, formed yellow crystals, m. p. 180·5—181·5° (Found: C, 52·1; H, 3·85; N, 10·1. $C_{36}H_{34}O_{14}N_6P_2$ requires C, 51·7; H, 4·1; N, 10·1%). The original residue, obtained in several such experiments, was heated under various conditions, without evidence of cyclisation: at 260—280°/0·3 mm. and also at 320—360°/0·3 mm., the main component of the distillate was unchanged dibromide, and an aqueous extract of the very dark residue again gave the above dipicrate. Replacement of benzene by chloroform in the initial reaction gave the same results.

(*b*) The condensation was repeated, using however phenyldiethylphosphine, in benzene and in chloroform. A portion of the glassy residue, treated as before, gave o-*xylylenebis(phenyldiethylphosphonium) dipicrate* (VI; R = Ph, R′ = Et, X = $C_6H_2O_7N_3$), yellow crystals, m. p. 159—160°, from acetone–ethanol (Found: C, 53·9; H, 4·4; N, 9·3. $C_{40}H_{42}O_{14}N_6P_2$ requires C, 53·8; H, 4·75; N, 9·4%). The residue, when heated at 340°/0·5 mm., gave a small distillate of phenyldiethylphosphine, identified by conversion into *dibromobis(phenyldiethylphosphine)-palladium*, yellow crystals, m. p. 135° (from ethanol) (Found: C, 40·3; H, 4·95. $C_{20}H_{30}Br_2P_2Pd$ requires C, 40·1; H, 5·1%).

Partheil and Gronover (*Ber.*, 1900, **33**, 606) using triethylphosphine (2 mols.) obtained the dibromide (VI; R = R′ = Et, X = Br), m. p. 250—250·5°; its behaviour on heating was not examined.

o-*Methoxymethylbenzyldiphenylphosphine* (XI).—A solution of diphenylphosphine (3·5 g.) in ether (20 c.c.) was added with stirring to one of sodium (0·5 g., 1 atom-equiv.) in liquid ammonia (70 c.c.), the deep blue colour of which changed to deep brown. A solution of *o*-methoxy-

methylbenzyl chloride (IX) (3·5 g., 1 mol.) in ether (10 c.c.) was then slowly added, the solution becoming orange and depositing a white solid. The ammonia was allowed to evaporate spontaneously and the residual ethereal solution was boiled under reflux in nitrogen for 2 hr. The cooled, filtered solution on distillation gave a colourless unidentified fraction, b. p. *ca.* 100°/0·15 mm., and then the phosphine (XI), b. p. 180—196°/0·15 mm., as an extremely viscous greenish oil (1·6 g., 30%), which was not further purified (Found: 76·5; H, 6·5. Calc. for $C_{21}H_{21}OP$: C, 78·7; H, 6·5%). It was characterised as its *methiodide*, colourless crystals, m. p. 130—131°, from methanolic ether (Found: C, 56·8; H, 5·3. $C_{22}H_{24}OIP$ requires C, 57·1; H, 5·3%).

2 : 2-*Diphenylisophosphindolinium Bromide* (XII).—A solution of the phosphine (XI) (1·6 g.) in acetic acid (70 c.c.) diluted with hydrobromic acid of constant b. p. (70 c.c.) was boiled under reflux for 2·5 hr. whilst hydrogen bromide was passed through. The solvents were then removed in a vacuum, giving a glassy residue of the crude bromide (XII). This was extracted with cold water (leaving a liquid constituent of pleasant odour), and the filtered extract again evaporated. The bromide was obtained as a semicrystalline highly hygroscopic residue which could not be readily purified. A portion, treated with sodium picrate, each in aqueous solution, deposited the *picrate* (as XII), beautiful lemon-yellow needles, m. p. 180—181°, from ethyl acetate (Found: C, 60·1; H, 4·1; N, 8·2. $C_{26}H_{20}O_7N_3P$ requires C, 60·3; H, 3·8; N, 8·1%

Diethyl-o-methoxymethylbenzylphenylphosphonium Salts (XIII).—A mixture of the chloride (IX) (2·5 g.) and phenyldiethylphosphine (2·3 g., 1 mol.) was gently warmed under nitrogen at atmospheric pressure; a vigorous reaction occurred, giving on cooling a thick almost solid syrup. This was the crude phosphonium chloride (XIII; X = Cl), for it was freely soluble in water and when treated with aqueous potassium iodide gave the *iodide* (XIII; X = I), colourless crystals, m. p. 113—114°, from ethanol–ether (Found: C, 53·0; H, 6·0. $C_{19}H_{26}OIP$ requires C, 53·2; H, 6·0%).

This iodide was also prepared by the interaction of *o*-methoxymethylbenzyl iodide (cf. p. 2820) with phenyldiethylphosphine (1 mol.) in acetone; addition of ether precipitated the iodide, m. p. 113—114° (alone and mixed) when crystallised as before.

The crude chloride, when heated in a vacuum under nitrogen ultimately to *ca.* 350°, underwent much charring whilst yielding a semicrystalline distillate, which when basified and extracted with benzene gave on distillation a main fraction of phenyldiethylphosphine, b. p. 104—106°/17 mm., and then a very small fraction, b. p. 170—180°/16 mm., a yellow oil which did not combine with methyl iodide and was apparently not a phosphine.

Palladium Derivatives of the Phosphine (III).—(A) *Monochlorobis-(2-phenylisophosphindoline)palladium.* A hot concentrated aqueous solution of potassium palladochloride was added to an excess of a hot ethanolic solution of the phosphine (III) and the mixture then gently boiled. The clear solution thus obtained was cautiously diluted with water and allowed to cool, pale yellow crystals separating. These were recrystallised from aqueous ethanol, and the solution on slow cooling deposited fine colourless crystals of the *monochloro*-derivative, m. p. 177—178° (Found: C, 59·35; H, 4·9; Pd, 18·0%; *M*, ebullioscopic in 0·481% ethanolic solution, 3310; in 1·595% acetone solution, 3410. $C_{28}H_{26}ClP_2Pd$ requires C, 59·35; H, 4·65; Pd, 18·0%; *M*, 566·4). The material used in each of the molecular-weight determinations was subsequently recovered unchanged.

When this material was again recrystallised from aqueous ethanol, the solution being however rapidly cooled and scratched, the *monochloro*-derivative separated as colourless crystals, m.p. 129—131° (Found: C, 59·3; H, 5·0%).

Dr. French reports: "The quantity of substance available (40 mg.) was insufficient to measure by the normal Gouy method, but a Faraday-type method was improvised and measurements were made in this way. These measurements indicated that the substance had a very small diamagnetic susceptibility of the order of $-0{\cdot}1 \times 10^{-6}$. However, on account of the comparative insensitivity of the method, the possibility of a very feeble paramagnetism could not unfortunately be entirely dismissed. Nevertheless, a compound of molecular weight approximately 500 with one unpaired electron would be expected to show a paramagnetic susceptibility of the order of 2×10^{-6}, and this possibility can, I think, be ruled out. Our general conclusion is that the substance is diamagnetic, the very low susceptibility being due to either (1) the presence of very small traces of a ferromagnetic impurity, or (2) a temperature-independent paramagnetism such as occurs in $KMnO_4$."

An acetone solution of a crude unrecrystallised sample of the monochloro-compound was gently evaporated during 2 hr., the process being twice interrupted for cooling and collection of a crop of the monochloro-compound; the final clear orange solution, when set aside, slowly

deposited brilliant yellow crystals of *dichlorobis-(2-phenylisophosphindoline)palladium*, m. p. 256—260° (decomp.) (Found : C, 56·0; H, 4·8. $C_{28}H_{26}Cl_2P_2Pd$ requires C, 55·85; H, 4·4%), which then appeared to be almost completely insoluble in boiling ethanol and acetone. The precise conditions determining the formation of this compound are at present unknown. It does not arise by the decomposition of the monochloro-compound, for an acetone solution of a pure sample of the latter was similarly boiled for 4 hr., and when evaporated to dryness yielded a residue of unchanged material, m. p. 176—178°. The dichloro-compound appears to be reasonably soluble in the initial crude aqueous-ethanolic solution, but, when once crystallised in the pure condition, to be almost insoluble in the usual organic solvents.

Similarly, another crude unrecrystallised sample of the monochloro-compound, when treated in dilute aqueous-ethanolic solution with aqueous potassium iodide, deposited *di-iodobis(2-phenylisophosphindoline)palladium*, deep crimson crystals, m. p. 246—248° after washing with boiling water and ethanol (Found : C, 43·3; H, 3·55. $C_{28}H_{26}I_2P_2Pd$ requires C, 42·8; H, 3·35%).

(B) *Monobromobis-(2-phenylisophosphindoline)palladium.* This was prepared as the monochloro-compound but with potassium palladobromide; dilution and cooling of the clear solution deposited scarlet crystals of the *monobromo*-compound, m. p. 196—198° (decomp.) after recrystallisation from aqueous ethanol (Found : C, 54·9; H, 4·5; Pd, 17·2. $C_{28}H_{26}BrP_2Pd$ requires C, 55·0; H, 4·3; Pd, 17·45%).

Dibromobis-(2-phenylisoarsindoline)palladium.—This *compound*, prepared in the usual way by heating an aqueous-ethanolic solution of potassium palladobromide and the arsine (2 mols.), formed orange-yellow crystals, m. p. 248—249° (decomp.) from acetone (Found : C, 43·4; H, 3·1. $C_{28}H_{26}Br_2As_2Pd$ requires C, 43·2; H, 3·4%).

Dibenzylphenylphosphine.—This preparation was performed under pure nitrogen throughout. A solution of benzylmagnesium chloride was prepared by the addition of benzyl chloride (50·4 g., 4 mols.) during 2 hr. to magnesium (10·2 g., 4·2 atom-equivs.) under ether (200 c.c.), the mixture being then stirred for a further 2 hr. It was then cooled in ice-water and vigorously stirred whilst a solution of phenyldichlorophosphine (17·9 g., 1 mol.) in benzene (100 c.c.) was added during 30 min., a vigorous reaction ensuing. The mixture was heated under reflux for 30 min., cooled, and hydrolysed with aqueous ammonium chloride, the organic layer then syphoned off and dried (Na_2SO_4) and the solvent removed, the residual dibenzylphenylphosphine readily crystallising on cooling.

Distillation under nitrogen gave the pure *phosphine* (24 g., 83%), b. p. 176—177°/0·3 mm., m. p. 71—72° (Found : C, 82·2; H, 6·4. $C_{20}H_{19}P$ requires C, 82·7; H, 6·6%). The m. p. was not increased by redistillation, sublimation, or recrystallisation from ethanol or benzene under nitrogen.

Even a cold ethanolic solution on exposure to the air rapidly deposited the oxide, m. p. 174° (Found : C, 78·3; H, 6·2. Calc. for $C_{20}H_{19}OP$: C, 78·4; H, 6·25%) : the infra-red absorption spectrum shows a band at 8·45 μ, confirming the P–O linkage.

The phosphine was further characterised by formation of the methiodide, m. p. 206—208° after crystallisation from ethanol. Meisenheimer *et al.* (*loc. cit.*) give m. p. 208°.

The phosphine under the usual conditions gives *dichlorobis(dibenzylphenylphosphine)-palladium*, yellow crystals, m. p. 230—231° (decomp.) (Found : C, 63·2; H, 5·3. $C_{40}H_{38}Cl_2P_2Pd$ requires C, 63·35; H, 5·1%), and the *dibromo*-analogue, pale yellow crystals, m. p. 240—242° (decomp.) (Found : C, 56·4; H, 4·2. $C_{40}H_{38}Br_2P_2Pd$ requires C, 56·7; H, 4·5%).

2-Phenylisoindoline Methopicrate.—The *iso*indoline was converted into the methiodide, m. p. 177° (Scholtz and Wolfrum, *Ber.*, 1910, **43**, 2304), which in turn gave the *methopicrate*, yellow crystals, m. p. 140—141°, from water (Found : N, 13·0. $C_{21}H_{18}O_7N_4$ requires N, 12·8%).

We are greatly indebted to Dr. J. A. Reid and Dr. C. M. French for their help in this investigation, and to the Department of Scientific and Industrial Research for a Grant (I. T. M.). A Senior Rouse Ball Studentship (I. T. M.) and a Rouse Ball Research Studentship (F. H. C. S.), awarded by Trinity College, are gratefully acknowledged.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 25th*, 1954.]

Fluorosulphonic Acid. Part I. Some Properties of the Aqueous Solution.

By A. A. Woolf.

[Reprint Order No. 5207.]

Aqueous solutions of the practically unhydrolysed acid can be prepared by passage of alkali fluorosulphonates through cation-exchange resins. The acid is shown to be a strong acid, by comparison with sulphuric acid in alkalimetric titrations. Conductivity measurements indicate a simple ionization to H_3O^+ and SO_3F^- in dilute solutions. The mobility of the latter ion is close to that of the perchlorate ion. The heat of ionization, 1·1 kcal. for 0·04M-solutions, indicates other species in more concentrated solutions.

The only two solvents of any general application for the preparation of simple and complex fluorides are hydrogen fluoride and bromine trifluoride. Since both have limitations, additional solvents are required to extend the range of preparations. Fluorosulphonic acid, first prepared by Thorpe and Kirman (*J.*, 1892, **61**, 921), may combine some of the desirable properties of hydrogen fluoride and sulphuric acid, and the present work aims at the elucidation of its solvent and general acid properties.

The only evidence previously advanced that fluorosulphonic acid was a strong monobasic acid was the existence of metal fluorosulphonates stable in the solid state and in solution. The lack of any quantitative measurements on the acid presumably arises from the difficulty in interpreting results on the hydrolysis mixture. The hydrolysis of the anhydrous acid according to the scheme $H{\cdot}SO_3F + H_2O = HF + H_2SO_4$ (Traube and Reubke, *Ber.*, 1921, **54**, 1618) has been confirmed by a complete analysis (it has also been shown that the anhydrous acid is a true compound and not a constant boiling-point mixture). In concentrated solutions an equilibrium is attained, the constant of which—calculated from concentrations—varies widely on dilution. Lange (*Z. anorg. Chem.*, 1933, **215**, 321), by examination of the effect of added acids and salts on the equilibrium, concluded that the equilibrium constant was not made up of two superimposed constants due to different forms of fluorosulphonic acid. The kinetics of the hydrolysis, however, are not incompatible with two hydrolysis mechanisms. The extent of the initial hydrolysis depends both on the method by which the water is added, and the quantity added; the slower the rate of addition and the lower the temperature, the less the hydrolysis. The hydrolysis subsequent to the initial instantaneous reaction is slow and it seems that the rate of fission of the sulphur–fluorine bond in the predominantly covalent structure of the anhydrous acid $HO–SO_2–F$ is more rapid than in the fluorosulphonate ion, $(O_3S–F)^-$. Thus part of the anhydrous acid could hydrolyse directly and the remainder be converted into a hydroxonium acid, which hydrolyses slowly even at high temperatures. There are practical limits to the velocity of addition of the anhydrous acid to water, and hence solutions free from appreciable sulphate and fluoride cannot be prepared in this way. It is possible to form solutions of the almost unhydrolysed acid by a displacement reaction of the alkali ions of the fluorosulphonates with the hydrogen ions on strongly acidic ion-exchange resins. The aqueous acid so formed is of the same order of stability as aqueous tetrafluoroboric acid (Wamser, *J. Amer. Chem. Soc.*, 1948, **70**, 1209; 1951, **73**, 409). It is more stable than the complex fluoro-acids of Group VA. The stability of the latter, when prepared on exchange resins, increase from hexafluoroantimonic to hexafluorophosphoric acid.

The pH values of the aqueous acid show that a 1 : 1 electrolyte is present in dilute solutions, because the values calculated for a complete ionization, with allowance for interionic attraction, agree with the experimental values. The well-known similarity in solubilities and crystallographic properties between perchlorates and fluorosulphonates means that these ions have similar radii in the solid state and are similarly solvated in solution. Hence the ionic mobility should be similar. The mobility of the fluorosulphonate ion was found from the equivalent conductivity at infinite dilution of potassium

fluorosulphonate, there being no reason to suppose that it ionizes differently in solution from the solid. The value obtained (71) is close to that of the perchlorate ion (69). By deducting this mobility from the equivalent conductivity of aqueous fluorosulphonic acid, the mobility of the hydroxonium ion should result if the species present in dilute solutions are indeed H_3O^+ and SO_3F^-. The value obtained was in satisfactory agreement with this ionization when the hydrolysis of the fluorosulphonate ion was considered. (Even potassium fluorosulphonate solutions have an acid reaction, and will precipitate insoluble sulphates when left in contact with barium or benzidine salt solutions.)

The species present in concentrated solutions may differ from those in dilute solutions. The heat of neutralization is 14·4(6) kcal. for 0·04M-solutions, so the heat of ionization, *viz.*, 1·1 kcal., although less than that of hydrofluoric or sulphuric acid at the same concentration (2·7 and 2·0 kcal., respectively), may indicate ions other than H_3O^+ and SO_3F^- in solution. One possibility is an ionization to H_3O^+ and $HS_2O_6F_2^-$. The latter ion can retain the preferred four-fold co-ordination of the sulphur oxy-acid anions if it has the structure $O_3S{-}SO_3(FHF)$. Concentrated solutions of fluorosulphonic acid can be prepared by freeze-drying and it is hoped to examine their properties.

Experimental

Analysis of Fluorosulphonic Acid and its Hydrolysate.—The problem is essentially that of analysing a F^-, $SO_4^{=}$, SO_3F^- mixture. Previous incomplete analyses are reported by Thorpe and Kirman (*loc. cit.*), Ruff and Braun (*Ber.*, 1914, **47**, 654), and Goddard, Hughes, and Ingold (*J.*, 1950, 2575).

0·5—1 Ml. of freshly distilled anhydrous acid were weighed in an all-glass syringe whose end was closed with a Polythene capillary and cap. The acid was slowly expelled under 200—500 ml. of carbon dioxide–free water in a Polythene bottle. Aliquot parts of 20—25 ml. were weighed in waxed beakers for analysis.

Analysis of hydrolysate. (i) Sulphate. Benzidine hydrochloride was shown to be specific for sulphate in the presence of fluoride and fluorosulphonate. Quantitative analyses of potassium sulphate solutions in the presence and absence of potassium and hydrogen fluorides agreed to 0·3%. The following volumetric procedure was adopted after trial experiments. 50 Ml. of reagent (9·35 g. of benzidine hydrochloride and 20 ml. of concentrated hydrochloric acid per l.) were added to 50 ml. of sulphate solution (*ca.* N/20 with respect to sulphuric acid). After 12 min. at 0° the precipitate was filtered on a pulp-pad (about ¼ of a No. 41, 12·5-cm. Whatman paper) supported by a Witt plate, and washed with 20 ml. of water at 0°. The pad and precipitate were suspended in hot water and titrated with N/10-alkali to the phenolphthalein end-point (Belcher, Nutten, and Stephen's 4-amino-4′-chlorobenzidine reagent could be used; *J.*, 1953, 1334).

(ii) Fluorosulphonate. Nitron acetate is specific for the fluorosulphonate ion in the mixture. 10 Ml. of 10% nitron in 20% acetic acid were added to the aliquot, and the whole kept at 0° for a few hours. The precipitate, washed with 20 ml. water at 0°, was dried at 120°.

(iii) Fluoride. The aliquot, neutralized to alizarin-red and buffered to pH 3 with chloroacetic acid–sodium chloroacetate, was titrated with a thorium nitrate solution standardized against fluoride solutions which had approximately the same sulphate content as the unknown.

(iv) Alkalimetric titration. This titration, which is possible because of the increase in acidity from 1 to 3 equivs. on hydrolysis, is the most accurate and is taken as the standard for comparison. The carbon dioxide-free aliquot portion in a platinum dish was titrated quickly in the cold with carbonate-free alkali with phenolphthalein as indicator. If x is the fraction of acid hydrolysed, the hydrolysis mixture contains $(1 - x)$ equiv. of HSO_3F, x of HF, and $2x$ of H_2SO_4. When $x = 1$, the total acid formed is 3 equiv., whence

$$\text{Titre obtained/titre for complete hydrolysis} = (1 + 2x)/3 = R \text{ and } x = (3R - 1)/2.$$

Comparison of the degree of hydrolysis calculated from the alkalimetric and other titrations will agree if the assumption that the hydrolysis is $H_2O + H{\cdot}SO_3F = HF + H_2SO_4$ is correct. The results are expressed as percentage degree of hydrolysis, the alkalimetric result being given first in each instance: $SO_4^{=}$, 51·6, 51·9; 53·3, 53·9; SO_3F^-, 55·2, 55·2; 53·3, 54·2; F^-, 53·3, 54·5; 58·1, 59·3. (The values for fluoride are high because about 1—2% of the fluorosulphonate ion is titratable with thorium nitrate.)

Analysis of the acid. (i) Total fluoride. This was found by Willard and Winter's method

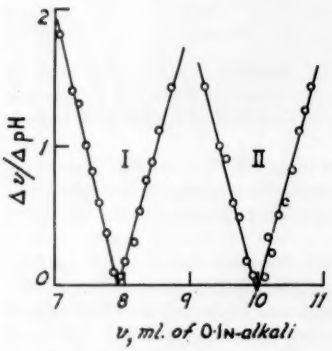
after addition of perchloric acid and steam-distillation. The thorium nitrate in this instance was standardized against a sodium fluoride solution treated in the above manner.

(ii) Total sulphate. The fluoride was removed by evaporation in glass at 133° in a slow stream of air. (A chlorobenzene constant-temperature jacket was used.) The residual sulphate was determined as barium sulphate.

$H{\cdot}SO_3F$ (g./100 g. H_2O)	% of total found F	% of total found SO_4	HF/SO_3	$H{\cdot}SO_3F$ (g./100 g. H_2O)	% of total found F	% of total found SO_4	HF/SO_3
(1) 0·561	100·0	99·5	1·005	(3) 0·488	99·6	99·9	0·997
(2) 0·361	99·3	99·4	0·999	(4) 0·395	99·8	99·9	0·999

The results were as shown in the above table: (1) and (2) were hydrolysates of the acid distilled at atmospheric pressure, (3) and (4) at approx. 10^{-4} mm.

Preparation of Aqueous Fluorosulphonic Acid.—Potassium fluorosulphonate, prepared from analytical-grade potassium persulphate and bromine trifluoride (Emeléus and Woolf, *J.*, 1950, 164), was powdered and heated at 150° *in vacuo* to remove all traces of solvent. The resultant salt was free from bromide, sulphate, and fluoride. When recrystallised from water the product was contaminated with sulphate. Solutions of up to 0·5 g. were passed through 5 g. (dry weight)



Curve I. 0·1084 g. of $K{\cdot}SO_3F$ passed through column: end-point found, 7·90 ml. of N/10-alkali (Calc.: 7·84 ml.); original normality of acid 0·0079; pH found, 2·15 (Calc.: 2·15). (The pH is calculated from the activity of the solution by use of the activity coefficient f derived from $-\log f = 0{\cdot}5\sqrt{I}$, where I is the ionic strength.)

Curve II. Titration of 10 ml. of 0·0998N-H_2SO_4 diluted to 100·05 ml.: end-point found, 10·00; pH found, 2·10 (Calc.: 2·09).

of Amberlite IR 120(H) resin in a Polythene column at the rate of 200 ml./hr. Blank runs with potassium sulphate solutions showed that the resin was unaffected by the fluorosulphonic acid formed. Larger quantities (up to 4 g. of KSO_3F) were passed through 20 g. of resin in a waxed glass column. The acid formed was estimated alkalimetrically, with the following results:

	KSO_3F added, g.	HSO_3F formed Found	HSO_3F formed Calc.		KSO_3F added, g.	HSO_3F formed Found	HSO_3F formed Calc.
Small column	0·2287	0·1146	0·1143	Large column	1·369	0·992	0·991
	0·1019	0·0740	0·0738		3·675	2·665	2·660

Properties of Aqueous Fluorosulphonic Acid.—The strength of the acid was shown by comparison of the neutralization curve with that of equivalent concentrations of sulphuric acid. The results of one such pair of titrations are illustrated on the derived $\Delta v/\Delta pH$–v curves (Gran, *Acta Chem. Scand.*, 1950, 559) shown here.

Comparison with Group V Fluoro-acids.—Potassium hexafluorophosphate (Emeléus and Woolf, *loc. cit.*) solution, after passage through an exchange column, gave a steady but higher titre than that required for HPF_6 (0·2034 g. required 12·05 ml. of N/10-alkali. Calc.: 11·04). This is due presumably to the rapid equilibration between HPF_6, HPO_2F_2, H_2PO_3F, and H_3PO_4. Direct passage of the eluant into excess of alkali still gave high results. The eluant from silver hexafluoroantimonate (Woolf and Emeléus, *J.*, 1949, 2865) solution hydrolysed on titration, but an approximate end-point was reached with 2·1 equiv. of alkali. The solution hydrolysed further to 3·2 equiv. in 20 days. By heating it at 100° in the presence of excess of alkali the hydrolysis was completed in a matter of minutes [Found: 7·10 equiv., *i.e.*, $HSbF_6 + 6H_2O \longrightarrow HSb(OH)_6 + 6HF$]. Fluorosulphonic acid solutions can be boiled for the same time with little change in titre.

Conductivity of Solutions.—The dilute solutions examined (less than 0·01M) were without action on Pyrex glass, the same conductivity values being found in a Polythene cell. The values obtained in the latter were of no great accuracy because of small air bubbles on the

surfaces and lack of absolute rigidity. De-ionized water of specific conductivity $0{\cdot}48 \times 10^{-6}$ mho was used. The Pyrex-glass cell had a constant of 5·985. The values in dilute solutions were difficult to reproduce, especially at lower concentrations, presumably because of hydrolysis (high values were obtained). The procedure was to prepare a concentrated solution (*ca.* 0·01M) and dilute this by weight in Polythene bottles immediately before measurement. The stock solution was rejected after 2 hr. Results were as shown below, concentration (C) being given in moles per 1000 g. of water, and conductivity (κ) in ohm^{-1}; $\Lambda = \kappa/C$.

Fluorosulphonic acid solutions at 25°.						*Potassium fluorosulphonate solutions at 25°.*					
10^3C	$10^4\kappa$	Λ	10^3C	$10^4\kappa$	Λ	10^3C	$10^5\kappa$	Λ	10^3C	$10^5\kappa$	Λ
0·6055	2·496	412	1·876	7·638	407	0·491	6·89	140·4	1·069	14·79	138·3
0·884	3·635	411	3·623	14·66	405	0·586	8·23	140·5	1·898	25·95	136·7
1·025	4·195	409	6·465	25·91	401	0·924	12·85	139·1	3·772	50·35	133·4

No solvent correction was applied in calculating the equivalent conductivities since all solutions were acidic. For fluorosulphonic acid solutions, the linear plot of Λ against $C^{\frac{1}{2}}$ leads to a Λ_0 value of 415·5, and for the salt solutions, a value of 144·5. The slopes calculated from Onsager's equation are in approximate agreement with the experimental values and it is considered that closer agreement would be fortuitous in view of the hydrolysis which occurs in dilute solutions.

Heat of Neutralization of the Aqueous Acid.—A Dewar-flask calorimeter was used. The alkali was added by piercing an ampoule suspended in the liquid. The values obtained were the same within experimental error in waxed and unwaxed vessels. The hydrolysis which occurred in the course of an experiment was not greater than 1%, and the results are significant to this accuracy. The solutions were handled, as a precaution, in waxed flasks before addition to the calorimeter. The results were:

Moles of H_2O per mole of $H{\cdot}SO_3F$	1,332	1,715	1,448	1,119
Heat of neutralization/mole (kcal.)	14·40	14·43	14·47	14·55

A mean value for a 0·039M-solution of 14·4(6) ± 0·1 is deduced (at 25°).

This work was carried out during the tenure of a Turner and Newall Fellowship.

THE UNIVERSITY, MANCHESTER. [*Received, March 15th*, 1954.]

Nucleotides. Part XXIX. Synthetic Uridine-Diphosphate-Glucose (UDPG).*

By G. W. KENNER, A. R. TODD, and R. F. WEBB.

[Reprint Order No. 5257.]

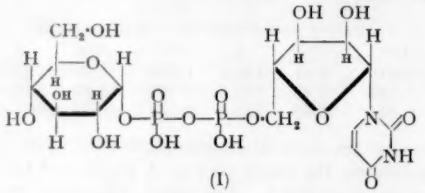
Reaction between di*cyclo*hexyl carbodi-imide and the pyridine salts of uridine-5′ phosphate and α-D-glucose-1 phosphate yields a complex mixture, which has been partially purified by chromatography on charcoal and paper. The final product has been shown to contain some 40% of uridine-diphosphate-glucose (UDPG) by direct comparison with material obtained from natural sources using paper chromatography, anion-exchange chromatography, and chemical degradations and by a specific enzymic assay.

RECENT investigation of the nucleotide fractions prepared from a number of plant and animal tissues has demonstrated the widespread occurrence of a group of substances which appear to be unsymmetrical P^1P^2-diesters of pyrophosphoric acid in which one of the esterifying groups is a ribonucleoside and the other a sugar or uronic acid derivative. Several of these substances are known to function as coenzymes. The best-known member of the group is uridine-diphosphate-glucose (UDPG), isolated from baker's yeast by Caputto, Leloir, Cardini, and Paladini (*J. Biol. Chem.*, 1950, **184**, 333) and subsequently detected in brewer's yeast, and in the liver, kidney, brain, and muscle of rats (Caputto *et al.*, *loc. cit.*), and in green plants (Buchanan, Lynch, Benson, Bradley, and Calvin, *J. Biol. Chem.*, 1953, **203**, 935). One function of UDPG is to act as a coenzyme in the system (galactowaldenase) which converts galactose-1-phosphate into glucose-1 phosphate, but it has been suggested

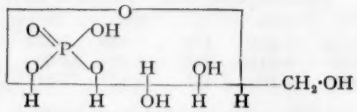
* Part XXVIII, *J.*, 1954, 2288.

(*e.g.*, by Benson, Calvin, *et al.*, *Phosphorus Metabolism*, 1952, **2**, 440) that UDPG may be an intermediate in the synthesis of polysaccharides. This is supported by recent observations of Leloir *et al.* on the enzymic synthesis of trehalose phosphate (Leloir and Cabib, *J. Amer. Chem. Soc.*, 1953, **75**, 5445) and of sucrose (Leloir and Cardini, *ibid.*, p. 6084).

Structure (I) for UDPG was advanced by Caputto *et al.* (*loc. cit.*) relying mainly on titration data and the results of acid hydrolysis. With alkali, UDPG gave uridine-5′ phosphate



(I)



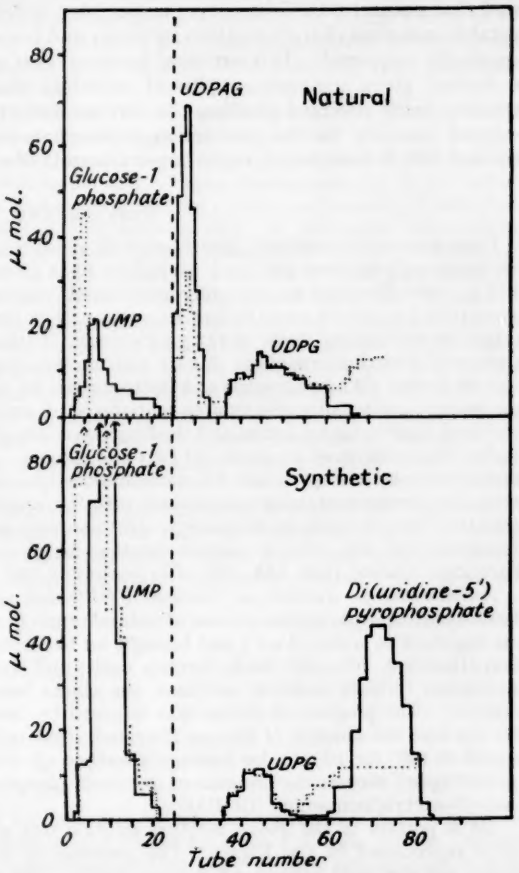
(II)

and a monobasic glucose phosphate formulated as the cyclic 1 : 2-phosphate (II) (Paladini and Leloir, *Biochem. J.*, 1952, **51**, 426). The formation of (II) was taken to indicate an α-configuration at $C_{(1)}$ in the glucose residue, since only in the α-form is the phosphate group in the *cis*-position with respect to the hydroxyl at $C_{(2)}$. This conclusion is also supported by the more recent finding that UDPG can be synthesised enzymically from uridine triphosphate and α-D-glucose-1 phosphate by uridyl transferase (Munch-Petersen, Kalckar, Cutolo, and Smith, *Nature*, 1953, **172**, 1036).

Although the structure (I) appeared very likely to be correct, it seemed worth while to confirm it by synthesis, as has been done in the case of flavin-adenine-dinucleotide (FAD) (Christie, Kenner, and Todd, *Nature*, 1952, **170**, 924; *J.*, 1954, 46). However, the extreme sensitivity of UDPG to both acid and alkali made it unlikely that any of the currently used protecting groups for the nucleoside or sugar components of the molecule could be removed in the final stages of synthesis without well-nigh total destruction of the coenzyme; the method of synthesis used for FAD was therefore not applicable to UDPG. Attention was turned instead to the direct dehydration of monoalkyl phosphates to P^1P^2-dialkyl pyrophosphates by means of di*cyclo*hexyl carbodi-imide ($C_6H_{11}\cdot N{:}C{:}N\cdot C_6H_{11}$) (Khorana and Todd, *J.*, 1953, 2257). It was already known that P^1P^2-di(uridine-5′) pyrophosphate could be prepared directly from pyridinium uridine-5′ phosphate in good yield by this method (Christie, Elmore, Kenner, Todd, and Weymouth, *J.*, 1953, 2947). Moreover, in an unpublished experiment, Dr. F. J. Weymouth had allowed di*cyclo*hexyl carbodi-imide (1·2 mols.) to react with a dimethylformamide solution of equimolar quantities of pyridinium uridine-5′ phosphate and pyridinium benzyl phosphate. Paper chromatography (Kenner, Todd, and Weymouth, *J.*, 1952, 3675; Christie *et al.*, *loc. cit.*) showed that the nucleotides in the reaction product consisted of P^1-uridine-5′ P^2-benzyl pyrophosphate (32%), P^1P^2-di(uridine-5′) pyrophosphate (16%), and unchanged uridine-5′ phosphate (52%). The condensation under similar conditions of the pyridinium salts of uridine-5′ phosphate and α-D-glucose-1 phosphate was therefore expected to give a mixture containing some (I). The situation is less favourable in this case, for pyridinium α-D-glucose-1 phosphate is converted by di*cyclo*hexyl carbodi-imide into the cyclic α-D-glucose-1 : 2 phosphate (II) amongst other products. The formation of cyclic uridine-2′ : 3′ phosphate from uridine-2′ and -3′ phosphates has likewise been detected by Dr. D. M. Brown in this laboratory, and, indeed, production of phosphate esters appears to be a general reaction of carbodi-imides under appropriate conditions (Weymouth, Ph.D. thesis, Cambridge, 1952; Khorana, personal communication). An excess of carbodi-imide had, therefore, to be avoided. A number of trials suggested that the most favourable reaction mixture was that of pyridinium uridine-5′ phosphate (1 mol.), pyridinium α-D-glucose-1 phosphate (1·9 mol.), and di*cyclo*hexyl carbodi-imide (1·7 mol.) in dimethylformamide. Paper chromatography showed this reaction mixture to be very complex but two of the components appeared to contain uridine, phosphate, and glucose residues.

Anion-exchange chromatography is generally a more powerful analytical method than paper chromatography and, through the courtesy of Dr. L. F. Leloir, we were able to apply

it to a sample of UDPG of natural origin. As shown in the Figure, the UDPG was clearly separated from uridine-5′ phosphate, glucose-1 phosphate, and uridine-diphosphate-*N*-acetylglucosamine: similar results have been recorded by Cabib, Leloir, and Cardini (*J. Biol. Chem.*, 1953, **203**, 1055), who used chloride instead of formate elution. Similar analysis of the synthetic product (see Figure) showed the presence of UDPG to the extent of some 3·5% of all the uridine compounds eluted. Attempted separation of a larger quantity for the purpose of final isolation was, however, unsuccessful, since the UDPG was evidently



Elution of mixtures containing UDPG of natural and synthetic origin from an anion-exchange column by 0·01M-formic acid–0·06M-ammonium formate (tubes 0—24), and 0·05M-formic acid – 0·25M-ammonium formate (tubes 25—85). Abscissa: number of 10·5 c.c. fractions. Ordinate: μmol. of uridine derivatives, assuming ε 10,000 at 260 mμ (———); μmol. of glucose after acid hydrolysis (.....).

decomposed on the column [cf. the decomposition of uridine-diphosphate-glucuronic acid (Storey, personal communication) and coenzyme A (Stadtman and Kornberg, *J. Biol. Chem.*, 1953, **203**, 47) on anion-exchange columns]. Recourse was therefore had to charcoal chromatography. No well-defined separation was achieved by this method but one fraction, on subsequent paper chromatography in two solvent systems, yielded an ammonium salt; this was estimated to contain about 42% of UDPG, which accounted for 68% of the nucleotide components of the material.

Dr. H. M. Kalckar kindly arranged for the synthetic material to be assayed by determination of the glucose-1 phosphate liberated on incubation with uridyl transferase and inorganic pyrophosphate (cf. Munch-Petersen *et al.*, *loc. cit.*); the results confirmed the finding that 40% of the uridine nucleotides were present as UDPG, whereas paper chromatography had given a value of 54% for this sample. In addition to this evidence of identity

and that of paper chromatographic comparison with UDPG of natural origin, we were able to show that acid and alkaline hydrolyses yielded the products already recorded as being given by the natural material.

Current interest in UDPG and its biological function leads us to present our results, although pure synthetic UDPG has not been isolated in solid form. The results show that a product has been obtained (as ammonium salt) containing 42% of UDPG identical chemically and biologically with the natural coenzyme, and the method of synthesis, despite the low yield, confirms the structure (I) which has been allotted to it. It should be borne in mind that natural UDPG has never as yet been isolated in a pure state, and that for such unstable materials characterisation by paper and ion-exchange chromatography in solution is normally employed. It is our view, however, that a suitable purification procedure could be devised, given adequate supplies of material; the working-out of such a procedure is, however, being deferred pending the further development of methods which have been designed specially for the production of unsymmetrical P^1P^2-diesters of pyrophosphoric acid and will, it is expected, make larger amounts of synthetic UDPG available.

Experimental

Condensation of Uridine-5′ Phosphate with α-D-Glucose-1 Phosphate using Dicyclohexyl Carbodi-imide.—Pyridinium uridine-5′ phosphate (0·45 g.) and pyridinium α-D-glucose-1 phosphate (0·72 g.) were dissolved in cold anhydrous dimethylformamide (40 c.c.), and the solution was concentrated at 50° *in vacuo* to half its volume, then cooled to room temperature. A solution of di*cyclo*hexyl carbodi-imide (0·412 g.) (Schmidt, Hitzler, and Lahde, *Ber.*, 1938, **71**, 1933) in a mixture of dimethylformamide (2 c.c.) and methyl cyanide (2 c.c.) was then added, and the mixture shaken till homogeneous and then set aside for 45 min. Water (15 c.c.) was next added and the precipitated di*cyclo*hexylurea centrifuged off and washed with water (3 × 10 c.c.). The combined supernatant solution and washings were evaporated under reduced pressure, and the residue was redissolved in water (30 c.c.) and filtered. Examination of the solution by paper chromatography in *iso*propanol–1% ammonium sulphate (2 : 1) indicated the presence of at least seven phosphorus-containing components with R_A ranging from 0·01—1 ($R_A = R_{adenosine}$ = distance travelled relatively to adenosine). Of these, only two ($R_A = 0·31, 0·45$) showed ultra-violet absorption and also gave a positive reaction for glucose with the aniline phthalate reagent (Partridge, *Nature*, 1949, **164**, 443) after heating to 100° with 0·02N-hydrochloric acid.

Anion-exchange Analysis of Natural UDPG and of the Preceding Reaction Solution.—(*a*) Barium uridine-diphosphate-glucose of natural origin (5 mg., kindly supplied by Dr. L. F. Leloir) was dissolved in water (5 c.c.) and brought on to a column (5·5 × 0·8 cm.) of anion-exchange resin (Dowex-2, 200—400 mesh, formate cycle) and elution was carried out with formic acid–ammonium formate buffered solutions, the eluate being collected in an automatic fraction-collector. The progress of elution was followed by determining the ultra-violet absorption at 260 mμ and the amount of glucose liberated when suitable portions, adjusted to pH 2, were heated at 100° for 10 min. by Somogyi's method (*J. Biol. Chem.*, 1951, **195**, 19). The elution curve (Figure) showed the presence of uridine-5′ phosphate (UMP), UDPG, and uridine-diphosphate-*N*-acetylglucosamine (UDPAG).

(*b*) A portion of the above reaction solution was similarly analysed and gave the elution curve reproduced in the Figure. The presence of uridine-diphosphate-glucose was clearly shown and the yield corresponded to *ca.* 3·5%. The nature of the other substances present, uridine-5′ phosphate (UMP), P^1P^2-diuridine-5′ pyrophosphate (DUP), and α-D-glucose-1 phosphate, was also checked by determining their elution positions separately on the same column with authentic pure specimens of these materials.

Charcoal Chromatography of Synthetic Material.—The main bulk of the reaction solution obtained above was put on a column (34 × 4 cm.) of mixed charcoal (Karbak grade; washed with 2N-hydrochloric acid, water, and ethanol; activated at 300°) and Hyflo Supercel (1 : 1), and the column was washed with water (1·2 l.). The column was eluted successively with 20%, 35%, and 50% aqueous ethanol (3·5, 3·5, and 1 l. respectively), and the eluates were collected in 18 c.c. fractions in an automatic collector. The fractions were examined for ultra-violet absorption at 260 mμ and for glucose liberated after heating at 100° for 10 min. with 0·01N-hydrochloric acid. Separation was very poor but most of the UDPG was found in the 35% ethanol eluate. Fractions 215—419 were combined, adjusted to pH 8 with aqueous barium hydroxide (0·18N), then neutralised with carbon dioxide, filtered, and concentrated to 3 c.c.

under reduced pressure. The solution so obtained was applied as bands on Whatman No. 1 filter paper, and the chromatograms were developed with 95% ethanol–M-ammonium acetate (75 : 30). The diffuse bands between R_A 0·42 and 0·47 were cut out and eluted with water, and the eluate was concentrated as before and again chromatographed as a band with 95% ethanol–M-acetic acid containing ammonia to pH 3·8 (75 : 30). The bands between R_A 0·6 and 0·7 were cut out, eluted with water, neutralised with ammonia (0·01N), and concentrated to small bulk (0·5 c.c.) at 30° under reduced pressure, and ethanol (4 c.c.) was added. The precipitated crude ammonium salt of uridine-diphosphate-glucose was collected, washed with ethanol (2 × 3 c.c.) and ether (3 c.c.), and dried at room temperature over phosphoric oxide. A further quantity of similar material was obtained by adding acetone to the mother-liquor, giving a total of 10·5 mg. Analysis by paper chromatography in the above two ethanol–ammonium acetate systems showed that UDPG accounted for some 68% of the ultra-violet absorbing (*i.e.*, nucleotidic) material, and about 42% of the total material.

Identification of Synthetic UDPG.—In addition to the ion-exchange analysis (Figure) and the evidence of biological activity, the following experiments were carried out.

(1) The crude synthetic ammonium salt (1 mg.) in water (0·1 c.c.) was treated with 1 drop of aqueous ammonia (*d* 0·880) and set aside for 30 min. Paper chromatography in two solvent systems showed degradation to uridine-5′ phosphate and the cyclic α-D-glucose-1 : 2 phosphate.

Solvent systems: *A*, Ethanol (75)–ammonia solution (30). *B*, Methanol (60)–ammonia solution (10)–water (30). R_P values: α-D-glucose-1 : 2 phosphate, *A* 0·55, *B* 0·66; α-D-glucose-1 phosphate, *A* 0·13 and 0·2, *B* 0·3; uridine-5′ phosphate, *A* 0·45, *B* 0·5; inorganic phosphate, *A* 0—0·01, *B* 0·46 and 0·6. The hydrolysed synthetic material showed spots with the same R_P values and other characteristics (ultra-violet absorption, glucose analysis, phosphorus content).

(2) The synthetic material (1 mg.) was heated for 10 min. at 100° with 0·01N-hydrochloric acid (1 c.c.). Examined by paper chromatography in two solvent systems, the resulting solution was shown by direct comparison to contain uridine-5′ phosphate and uridine-5′ pyrophosphate. By eluting the spots from a paper chromatogram (run in solvent system *D* below) with 0·01N-hydrochloric acid and measuring the relative optical densities at 260 mμ it was found that the relative molecular proportions of uridine-5′ pyrophosphate and uridine-5′ phosphate were 1·2 : 1.

Another portion of the synthetic product (1 mg.) was heated for 10 min. at 100° with N-hydrochloric acid (1 c.c.). Paper chromatography showed that the hydrolysis solution contained uridine-5′ phosphate as the sole light-absorbing material. Paper chromatography (see Table): system *C*, *iso*propanol (20)–1% ammonium sulphate (10); system *D*, *n*-butanol (50)–acetic acid (20)–water (30).

	R_P values in system	
	C	*D*
Barium uridine-5′ pyrophosphate	0·29	0·16
Barium uridine-5′ phosphate	0·45	0·29
Product of 0·01N-acid hydrolysis:		
(*a*) uridine-5′ pyrophosphate	0·28	0·16
(*b*) uridine-5′ phosphate	0·45	0·28
Product of N-acid hydrolysis	0·46	0·28

(3) A sample of synthetic material was run side by side with natural UDPG supplied by Dr. L. F. Leloir, with the solvent systems *E* and *F* and gave the following results. Solvent systems used: *E*, 95% ethanol (75)–M-ammonium acetate (30); *F*, 95% ethanol (75)–M-acetic acid with ammonia to pH 3·8 (30).

	$R_{adenosine}$ in system		% of total uridine
	E	*F*	in system *E*
Natural UDPG:			
(*a*) uridine-5′ phosphate	0·33	0·81	57
(*b*) UDPG	0·43	0·64	22·5
(*c*) UDP-*N*-acetylglucosamine	0·55	0·72	20·5
Synthetic UDPG:			
(*a*) uridine-5′ phosphate	0·34	0·80	46
(*b*) UDPG	0·43	0·64	54

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The Kinetics of Alkyl–Oxygen Fission in Ester Hydrolysis. tert.-*Butyl 2 : 4 : 6-Trimethylbenzoate in Aqueous Ethanol.*

By V. R. Stimson and E. J. Watson.

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The kinetics of the acid-catalysed hydrolysis of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate have been studied in various water–ethanol mixtures, at various acid concentrations and at three temperatures. The Arrhenius equation is accurately followed but the values of E and A are significantly different from those found in the "normal" hydrolysis of esters. The variation of rate with solvent composition usually found in acid-catalysed reactions in this solvent is observed.

Four possible mechanisms for the acid-catalysed hydrolysis of esters, together with their steric and electronic requirements, have been described by Day and Ingold (*Trans. Faraday Soc.*, 1941, **37**, 686). Esters of primary alcohols are most commonly hydrolysed in acid conditions *via* mechanism $A'2$ which involves attack by a water molecule on the carbonyl-carbon atom of the esterium ion and is thus highly sensitive to steric effects at this position. Mechanism $A'1$ involves as key intermediate a stable acylium ion, $R\overset{+}{C}O$. In general, esters of the sterically hindered 2 : 4 : 6-trimethylbenzoic acid resist hydrolysis in aqueous or alcoholic solvents, *i.e.*, by mechanism $A'2$, and form the acylium ion only in such solvents as pure sulphuric acid. Mechanisms $A''1$ and $A''2$ involve alkyl–oxygen fission, $A''1$ being insensitive to steric hindrance but demanding strong electron release from the alkyl group. Cohen and Schneider (*J. Amer. Chem. Soc.*, 1941, **63**, 3382) have shown that *tert.*-butyl 2 : 4 : 6-trimethylbenzoate is readily hydrolysed in acidic aqueous and alcoholic media, and further, have proved that alkyl–oxygen fission is involved in alcoholysis, *tert.*-butyl methyl ether being obtained in neutral methanol, and a quantitative yield of 2 : 4 : 6-trimethylbenzoic acid, not the methyl ester, in methanolic hydrogen chloride, and we have assumed that alkyl–oxygen fission also occurs in aqueous ethanol. To distinguish kinetically between mechanisms $A''1$ and $A''2$ it is necessary to measure the variation of rate with water concentration. Mechanism $A''1$ seems more likely by analogy with the well-known unimolecular hydrolysis of the *tert.*-butyl halides; further the *tert.*-butyl group is electron releasing and hence meets the requirement of this mechanism. The mechanism may be formulated thus:

$$\text{Mes·COOBu}^t + \text{H}^+ \underset{\text{fast}}{\overset{\text{fast}}{\rightleftharpoons}} \text{Mes·C}\overset{+}{\text{O}}\text{HBu}^t \quad \ldots\ldots\ldots (1)$$

$$\text{Mes·C}\overset{+}{\text{O}}\text{HBu}^t \xrightarrow{\text{slow}} \text{Mes·COOH} + \overset{+}{\text{Bu}}{}^t \quad \ldots\ldots\ldots (A''1)\ (2)$$

$$\overset{+}{\text{Bu}}{}^t + \text{OH}_2 \xrightarrow{\text{fast}} \text{Bu}^t\overset{+}{\text{O}}\text{H}_2 \xrightarrow{\text{fast}} \text{Bu}^t\text{OH} + \text{H}^+ \quad \ldots\ldots\ldots (3)$$

where Mes denotes 2 : 4 : 6-trimethylphenyl.

Step (1) is the fast reversible addition of a proton to form the esterium ion, which slowly undergoes alkyl–oxygen fission in the rate-controlling step (2). The kinetic consequence is that $dx/dt \propto [\text{H}^+][\text{ester}]$; *i.e.* in a medium of constant hydrogen-ion concentration, the rate, is of first order in ester, and the first-order rate constants (k_1) so obtained are proportional to the catalyst concentration.

Experimental

Preparation of Materials.—*tert.*-Butyl 2 : 4 : 6-trimethylbenzoate, prepared as described by Cohen and Schneider (*loc. cit.*), who report b. p. 114—115°/3 mm., d^{23} 0·9654, n_D^{23} 1·4920, was fractionated twice and then had b. p. 96°/0·6 mm., d_4^{15} 0·970, n_D^{15} 1·4932.

Ethanol (2 l.) was successively distilled from concentrated sulphuric acid (25 c.c.) and sodium

hydroxide (10 g.), then refluxed with magnesium ethoxide (from 10 g. of magnesium in 200 c.c. of dry ethanol) for 4 hr., and distilled. The first 100 c.c. were rejected in each distillation.

Solvents.—The various solvent mixtures were made from measured volumes of ethanol and distilled water, and the compositions checked by density measurements. Stock aqueous ethanolic solutions of hydrogen chloride were made by bubbling the gas from "AnalaR" sodium chloride and concentrated sulphuric acid into each solvent mixture.

Kinetic Measurements.—At 77° and 85° the thermostat was constant to better than 0·1° but at 97°, where a boiling-water bath was used, the temperature varied between runs over several tenths of a degree owing to changes in the barometric pressure. As no consequent systematic variation in k_1 was observed a mean temperature was taken.

Measured portions (5 c.c.) of solutions of the ester of known concentration, from which a was calculated, were pipetted into Pyrex-glass bulbs which were sealed and placed in the thermostat. After a measured time the total acid content was determined by titration with 0·01N-baryta, the increase in titre above that at zero time giving x. The rate constant k_1 was then calculated from the formula $k_1 = (1/t) \log_e a/(a - x)$, 10—20 values being obtained from each run. Because 2 : 4 : 6-trimethylbenzoic acid is not esterified by ethanol in the presence of hydrogen chloride, the hydrolysis was not reversible and the straightforward first-order equation was adequate.

Titrations.—Constant-boiling hydrochloric acid consistent with "assay" silver was used as standard. The end-point to phenolphthalein in 0·01N-solution was sharp in freshly boiled distilled water in an atmosphere of nitrogen. Volumetric glassware was standardised. No correction for the expansion of the solvent was made to the concentration terms as calculation showed that the resulting correction to E did not exceed the experimental error.

Corrections due to the Reaction of the Catalyst with the Solvent.—Bird, Hughes, and Ingold (*J.*, 1943, 258), using 0·1N-solutions in 88% ethanol at 75°, found a considerable decrease in rate constant after about 50% reaction, due to the liberated hydrogen bromide reacting with the solvent. To obviate this difficulty Timm and Hinshelwood (*J.*, 1938, 863), working at temperatures up to 150° with the more slowly hydrolysed ethyl benzoate, used benzenesulphonic acid; however with 0·01N-acid, only in 100% ethanol at 97° was the removal of acid so large that a simple correction did not yield a consistent value of k_1. Experiments with the acidified solvent alone were run in parallel with the hydrolysis and the decrease of titre was observed. A corresponding correction was then made, amounting to 2 and 6% of x in 80 and 90% ethanol at 97°, respectively. In 100% ethanol at 97° the rate constant for the removal of acid by ethanol was determined ($k_1 = 5{\cdot}3 \times 10^{-3}$ min.$^{-1}$, when $[HCl]_{t=0} = 0{\cdot}0127$) and found to be *ca.* 1/3 of the rate of the hydrolysis. In these circumstances the correction was about 30%, and a hydrolysis rate constant accurate to only *ca.* 1/5 was obtained. In the remaining runs no correction was necessary.

The following are typical runs, with and without corrections.

a in mole/bulb. Temp. 97·3°. Baryta 0·01160N.

Solvent: 60% EtOH; $a = 7{\cdot}40 \times 10^{-5}$; [HCl] = 0·0101; [ester] = 0·0148.

No correction

Time (min.)	Titre (c.c.)	$10^3 k_1$ (min.$^{-1}$)
0	4·36	—
35	5·57	5·9
50	6·00	5·9
61	6·33	6·0
75	6·71	6·1
100	7·24	5·9
139	7·92	5·9
160	8·28	5·9
192	8·74	6·0
220	9·03	6·0
254	9·27	5·8
	Mean	5·9

Solvent: 90% EtOH; $a = 7{\cdot}80 \times 10^{-5}$; [HCl] = 0·0093; [ester] = 0·0156.

Correction = $+ 6 \times 10^{-4}$ c.c./min.

Time (min.)	Titre (c.c.)	Titre (corr.) (c.c.)	$10^3 k_1$ (min.$^{-1}$)
0	4·00	4·00	—
90	5·18	5·23	2·25
150	5·82	5·90	2·24
210	6·41	6·53	2·25
281	7·02	7·18	2·27
339	7·34	7·53	2·20
409	7·74	7·98	2·19
433	7·91	8·16	2·24
474	8·09	8·35	2·20
		Mean	2·23

Results and Discussion

The rate of hydrolysis of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate is directly proportional to the concentration of the acid catalyst and of the ester (cf. Table 1): this is consistent with, but not conclusive for, mechanism $A''1$. No uncatalysed solvolytic reaction was

detected (cf. Fig. 1). The Arrhenius equation $k_1/c_A = A_{Arr.}e^{-E_{Arr.}/RT}$ is accurately followed and $E_{Arr.}$ is independent of solvent composition (cf. Table 2). The variation of rate with solvent composition is not great, *e.g.*, the factor for change from 60% to 80% aqueous ethanol is 2·0.

TABLE 1. *First-order rate constants (k_1) for the hydrolysis of* tert.-*butyl* 2 : 4 : 6-*trimethylbenzoate.*

(C_A and C_E are the concentrations of hydrochloric acid and ester.)

Ethanol (% by vol.)	Temp.	10^3C_A (mole/l.)	10^3C_E (mole/l.)	10^3k_1 (min.$^{-1}$)	$10k_1/C_A$ (min.$^{-1}$ l. mole^{-1})	10^3C_A (mole/l.)	10^3C_E (mole/l.)	10^3k_1 (min.$^{-1}$)	$10k_1/C_A$ (min.$^{-1}$ l. mole^{-1})
60	97·3°	2·73	1·45	15·6	5·7	0·413	0·96	2·4	5·8
		1·71	2·43	9·8	5·7	0·406	1·38	2·5	6·1
		1·52	1·53	8·8	5·8	0·356	0·56	2·2	6·2
		1·01	1·48	5·9	5·8				
70	97·3	1·94	1·30	7·4	3·8	0·99	1·46	3·8	3·8
80	97·3	1·90	0·78	5·0	2·6	1·09	1·18	2·9	2·7
		1·61	1·54	4·6	2·8	0·76	0·95	2·1	2·8
		1·63	0·86	4·2	2·6	0·58	1·00	1·7	2·9
		1·45	0·83	4·1	2·8	0·160	1·69	0·46	2·9
		1·15	1·07	3·3	2·9				
91	97·3	1·88	1·24	4·5	2·4	0·93	1·56	2·2	2·4
100	97·3	1·27	1·68	17	13				
60	85·4	1·09	1·60	1·69	1·55	0·51	1·51	0·77	1·52
80	85·4	2·34	1·43	1·69	0·72	1·14	1·46	0·89	0·78
91	85·1	1·98	1·33	1·19	0·60				
60	77·7	2·08	1·51	1·30	0·63	1·10	1·43	0·72	0·65
70	76·8	0·88	1·27	0·31	0·35				

TABLE 2.

Ethanol (% by vol.)	$E_{Arr.}$ (kcal./mole)	$\log_{10}A_{Arr.}$ (A in sec.$^{-1}$)	$\Delta S^{\ddagger}_{97°}$ (cal. mole^{-1} deg.$^{-1}$)	Ethanol (% by vol.)	$E_{Arr.}$ (kcal./mole)	$\log_{10}A_{Arr.}$ (A in sec.$^{-1}$)	$\Delta S^{\ddagger}_{97°}$ (cal. mole^{-1} deg.$^{-1}$)
60	29·4	15·5	9·9	80	29·1	15·2	8·5
70	29·8	15·3	8·9	90	29·8	15·1	8·1
Mean	29·5						

$\log_{10} A$ was calculated by using the average value of E.

The Rate of the Reaction.—The value of $\log_{10}(10^6k_1/c_A)$ (sec.$^{-1}$) is 4·1 in 60% ethanol at 100°. Timm and Hinshelwood (*loc. cit.*) list 13 values ranging from 4·0 to 0·7 for the ethyl esters of substituted aromatic and aliphatic acids. For benzoic and *p*-toluic esters the values are 1·95 and 1·89. The acid hydrolysis of *tert.*-butyl 2 : 4 : 6-trimethylbenzoate is thus as fast as that of ethyl acetate and over a hundred times as fast as those of ethyl benzoate and *p*-toluate at 100°.

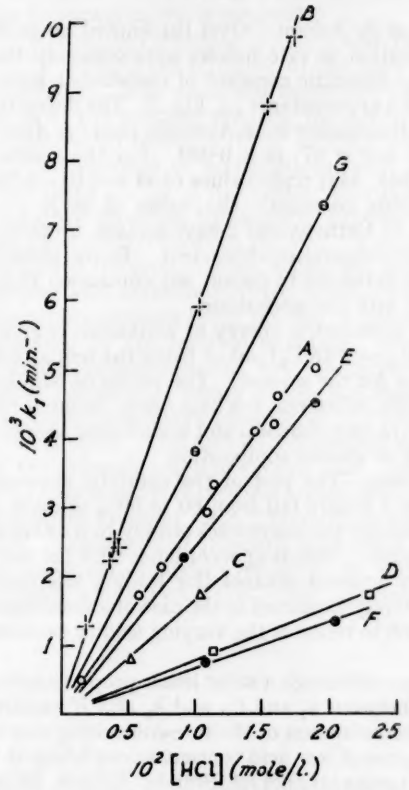
The Value of $E_{Arr.}$.—The magnitude of E is significantly different from those found in the normal acid hydrolysis of esters involving acyl–oxygen fission. Timm and Hinshelwood (*loc. cit.*) and Newling and Hinshelwood (*J.*, 1936, 1357) found values of 17—21 kcal./mole for the methyl and ethyl esters of various benzoic acids in 60% ethanol and 60% acetone; Davies and Evans (*J.*, 1940, 339) and Smith and Steele (*J. Amer. Chem. Soc.*, 1941, **63**, 3466) found 15—17 kcal./mole for ethyl esters of aliphatic acids in 70% acetone; and Tommila and Hinshelwood (*J.*, 1938, 1806) and Newling and Hinshelwood (*loc. cit.*) found 14—17 kcal./mole for various benzyl and phenyl acetates in 60% acetone. Timm and Hinshelwood (*loc. cit.*) have shown that electron-releasing groups (*e.g.* methyl) attached to the benzoic acid raised the activation energy for the ethyl benzoates. The increase is of the order of 0·1 kcal./mole for one methyl group, and it is not likely therefore that the present value of 29 kcal./mole can be explained in this way.

A well-known reaction that involves the rupture of an alkyl–oxygen bond is the formation of an alkyl halide from an alcohol. Hinshelwood (*J.*, 1935, 599) has studied the reaction of methanol and *tert.*-butanol with hydrogen chloride, and Bennett and Reynolds (*J.*, 1935, 131) that of methanol with hydrogen bromide. The reactions have activation

energies of 26—27 kcal./mole. For the reaction of ten higher aliphatic alcohols of both straight and branched chains Bennett and Reynolds (*loc. cit.*) find activation energies of 29—31 kcal./mole. These values are in contrast to those found in the reaction of an alcohol with a carboxylic acid, which involves acyl–oxygen fission, viz. 10—15 kcal./mole, but are comparable with the present value.

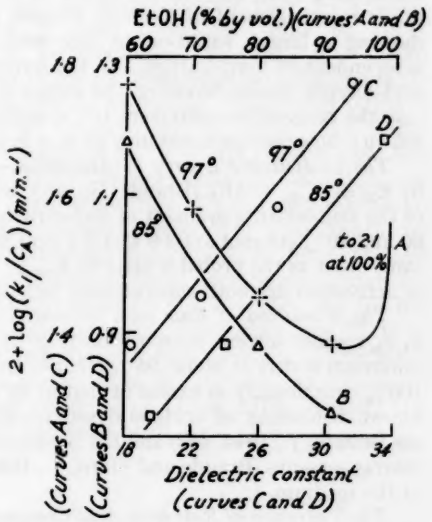
An interesting contrast between alkyl–oxygen and acyl–oxygen fission is shown in the rearrangement and hydrolysis of 1-ethynylbut-2-enyl acetate (Braude, *J.*, 1948, 795) in

FIG. 1.



A, 80% EtOH, 97° C. *E*, 91% EtOH, 97° C.
B, 60% ,, 97° C. *F*, 60% ,, 77° C.
C, 60% ,, 85° C. *G*, 70% ,, 97° C.
D, 80% ,, 85° C.

FIG. 2.



aqueous dioxan. As far as the positions of the ruptured and newly formed alkyl–oxygen bonds are concerned this rearrangement bears the same relation to Day and Ingold's mechanism *A*"2 (*loc. cit.*) as does S_N2' to S_N2 (de la Mare, Hughes, and Vernon, *Nature*, 1952, **169**, 672) but because of the strongly electron-attracting ethynyl group the hydrolysis is normal. For the hydrolysis $E_{Arr.} = 19$—20 kcal./mole whereas for the rearrangement $E_{Arr.} = 27$—28 kcal./mole.

The Value of $A_{Arr.}$.—$\text{Log}_{10}A_{Arr.}$, shown in Table 2, has the value 15—16. This is of a different order from that found in the normal acid hydrolysis of esters. Tommila and Hinshelwood, Timm and Hinshelwood, and Davies and Evans (*locc. cit.*) find values for $\log_{10}PZ$ of 7—8, 5—8, and 6—8, respectively. For anionotropic rearrangements Braude

and Jones (*J.*, 1946, **122**, 128) and Braude and Stern (*J.*, 1947, 1096) find $\log_{10}A = 13$—18 (32 cases with 2 exceptions). A is related to the entropy of activation by the expression $A = ekT/he^{\Delta S^{\ddagger}/R}$ (Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill, 1941, p. 417). The values of $\Delta S^{\ddagger}$, tabulated in Table 2, are substantially constant with varying solvent composition. The positive value of 8—10 cal. mole^{-1} deg.$^{-1}$ contrasts with the negative value of 14—16 cal. mole^{-1} deg.$^{-1}$ found by Braude (*loc. cit.*) in the hydrolysis of 1-ethynylbut-2-enyl acetate, which involves acyl–oxygen fission, but is comparable with the value found for the rearrangement which involves alkyl–oxygen fission. The positive value is also consistent with the proposed unimolecular mechanism.

Variation of Rate with the Dielectric Constant of the Solvent.—Over the limited range of solvent composition, 60—90% ethanol, the variation in rate follows approximately the relation, $\log_{10}(k_1/C_A) = mD + n$, where D is the dielectric constant of the alcohol–water mixture at the temperature concerned, and m and n are constants (cf. Fig. 2). The dielectric constants were obtained by interpolation and extrapolation from Akerlöf's data (*J. Amer. Chem. Soc.*, 1932, **54**, 4130). At 85° $m = 0{\cdot}029$ and at 97° $m = 0{\cdot}030$. For the anionotropic rearrangement of alcohols, Braude (*J.*, 1944, 444) finds values of $m = 0{\cdot}04$—$0{\cdot}06$, showing a larger variation of rate with dielectric constant; the value of m is also independent of temperature. In the hydrolysis of 1-ethynylbut-2-enyl acetate, involving acyl–oxygen fission, however, the values of m are temperature-dependent. In the present case the range of measurement is not sufficiently extensive to permit any conclusion to be drawn; however the constancy of m is in accord with the mechanism.

The Isodielectric Energy of Activation.—The isodielectric energy of activation is given by $E_D = E_{exp.} + \Delta E_D$ (Braude, *loc. cit.*), where $E_D = 2{\cdot}3RT_1T_2mb$, b being the magnitude of the temperature gradient of dielectric constant for the solvent. The values of ΔE_D for 60 and 80% ethanol are 3·0 and 2·5 kcal./mole, the difference, 0·5 kcal./mole, being of the same order as the probable error in $E_{exp.}$. Thus the experimental and isodielectric energies of activation are both substantially independent of solvent composition.

The Variation of Rate with Solvent Composition.—The plot of the catalytic constant k_1/c_A against solvent composition (Fig. 2) shows a steady fall from 60 to 90% ethanol, a minimum occurs at about 95% ethanol and thereafter the curve rises steeply to a value at 100% considerably in excess of that at 60% ethanol. This is in accordance with the well-known behaviour of acid-catalysed reactions in aqueous ethanol (for leading references see Braude, *J.*, 1944, **443**) and has been quantitatively explained in the case of anionotropic rearrangements (Braude and Stern, *J.*, 1948, 1982) in terms of the varying acidity function of the medium.

The Variation of Rate with Acid Concentration.—Although a strict linear proportionality holds between k_1 and C_A (Fig. 1) the relations between k_1 and C_A and k_1 and H (acidity function), derived by Braude (*loc. cit.*) for the determination of the rate-controlling step in an analogous system, are not diagnostic in the present low acid concentrations where it is likely that $H = n \log C_A + m$ and $n \approx 1{\cdot}00$ in aqueous ethanol (cf. Braude, *J.*, 1948, 1973).

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Some Heterocyclic Structures derived from Acenaphthene.

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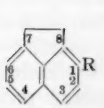
The conversion of 1-, 2-, and 3-aminoacenaphthene into some acenaphtheno-pyridine, -quinoline, and -*iso*quinoline derivatives is reported.

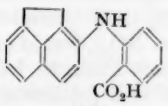
Conversion of 1-, 2-, and 3-aminoacenaphthene into some heterocyclic structures, required for biological study, is reported.

Morgan and Harrison (*J. Soc. Chem. Ind.*, 1930, **49**, 413T) obtained 1-nitroacenaphthene (I; R = NO_2) by nitration of the hydrocarbon with acetyl or benzoyl nitrate in acetic anhydride. This method is unsuitable for large-scale work and indeed, in our hands, gave none of the required product, the 3-nitro-isomer alone being isolated. We consequently studied other routes to (I; R = NH_2), ultimately preparing it from 1-acetylacenaphthene.

Condensation of acenaphthene with acetic acid–hydrogen fluoride gave 1-acetylacenaphthene (I; R = Ac) (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272), smoothly oxidised by sodium hypochlorite to 1-acenaphthoic acid (I; R = CO_2H) (cf. Fieser and Hershberg, *loc. cit.*). Esterification of the last compound with diazomethane furnished the methyl ester, which was converted into the hydrazide. Successive action of nitrous acid and dilute hydrochloric acid, however, failed to give (I; R = NH_2), *s*-di-1-acenaphthenylurea being the sole product. Formation of (I; R = NH_2) in low yield was achieved by the reaction sequence: (I; R = CO_2H) ⟶ acid chloride ⟶ azide ⟶ 1-aminoacenaphthene (*ca.* 30%) (admixed with larger quantities of *s*-di-1-acenaphthenylurea). Somewhat better results followed Beckmann rearrangement of 1-acenaphthenyl methyl ketoxime with phosphorus pentachloride, 1-acetamidoacenaphthene being obtained in 40% yield. The preparative method finally adopted was based upon Smith's extension of the Schmidt reaction (Smith, *ibid.*, 1948, **70**, 320) in which (I; R = Ac) was treated with sodium azide in molten trichloroacetic acid to give 1-acetamidoacenaphthene (I; R = NHAc) in excellent yield. Hydrolysis was best accomplished with alcoholic hydrochloric acid. Concentrated sulphuric acid could not be employed in this instance, as immediate sulphonation occurred even at 0° [cf. our earlier attempts (*J.*, 1948, 1713) to effect the Schmidt reaction on (I; R = Ac) in concentrated sulphuric acid].



(I)



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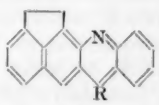

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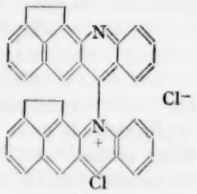


(IV)

Attempts to convert 1-aminoacenaphthene (I; R = NH_2) into pyrido(2′ : 3′-1 : 2)-acenaphthene proved wholly unsuccessful. Thus the normal conditions of the Skraup reaction led to extensive decomposition with recovery of a trace of unused base. No better results derived from (i) the addition of ferrous sulphate and/or boric acid (cf. Cohn, *J. Amer. Chem. Soc.*, 1930, **52**, 3685), (ii) the replacement of nitrobenzene as oxidant by arsenic oxide, or (iii) the substitution of 1-acetamidoacenaphthene for the base under the "mild" conditions recommended by Manske and his co-workers (*Canad. J. Res.*, 1941, **19**, *B*, 318). Condensation with paraldehyde or with acetaldehyde–pyruvic acid were likewise unsuccessful.

1-Aminoacenaphthene and *o*-chlorobenzoic acid condensed readily in amyl-alcoholic solution in the presence of copper bronze to give *N*-1′-acenaphthenylanthranilic acid (II). Ring closure of this compound to the corresponding acridine analogue could not be

achieved by concentrated sulphuric acid at 100° which caused rapid sulphonation (cf. above) or by phosphoric oxide in syrupy phosphoric acid at 150°, which was without effect. Reaction with phosphorus oxychloride led to a dark red crystalline compound which, though giving analyses correct for the expected 4′-chloroacenaphtheno(1′ : 2′-2 : 3)-quinoline (III; R = Cl), is probably best formulated as 1-[acenaphtheno(1′ : 2′-2 : 3)-4-quinolyl]-4-chloroacenaphtheno(1′ : 2′-2 : 3)quinolinium chloride (IV). Thus the red colour, relatively high melting point, and low alcoholic solubility accord well with the structure (IV). Again, reduction with sodium amalgam, zinc dust and acetic acid, or aluminium foil in ethanol led only to unidentified amorphous products of high melting point. Finally, the electrical conductivity of the compound in nitrobenzene at room temperature was approximately 20 times that of an equimolar solution of phenol, an observation which argues a high degree of ionisation. Distillation of the red quaternary salt (IV) with zinc dust under reduced pressure led to the formation of acenaphtheno-(1′ : 2′-2 : 3)quinoline (III; R = H) in low yield. The bright red colour of this base accords with the established effect of the heterocyclic nitrogen atom on the colour of linear polycyclic systems.

Attempts to extend Hollingsworth and Petrow's tetrahydrophenanthridine synthesis (*J.*, 1948, 1537) to 1-aminoacenaphthene were not successful.

Preparation of 2-aminoacenaphthene proved troublesome. Morgan and Harrison (*J. Soc. Chem. Ind.*, 1930, **49**, 413T) prepared this compound by the following reaction sequence: 3-formamidoacenaphthene ⟶ 3-amino-2-nitroacenaphthene ⟶ 3-iodo-2-nitroacenaphthene ⟶ 2-aminoacenaphthene, but the overall yields were low.

In our hands, nitration of 3-formamidoacenaphthene seldom gave yields approaching the 75% claimed by Morgan and Stanley (*ibid.*, 1925, **44**, 493T). In an attempt to improve this stage, 3-toluene-*p*-sulphonamidoacenaphthene was prepared and nitrated but the yield of 2-nitro-amine was no better. The conversion of this nitro-amine into 3-iodo-2-nitroacenaphthene proved highly unsatisfactory, even under the modified diazotisation conditions of Hodgson and Walker (*J.*, 1933, 1620) and had perforce to be abandoned. The improved porcedure ultimately adopted was to reduce the diazonium salt from 3-amino-2-nitroacenaphthene with cuprous oxide in methanol at 60° (Hodgson and Turner, *ibid.*, 1942, 748) to 2-nitroacenaphthene, which was conveniently hydrogenated to 2-amino-acenaphthene with hydrogen–platinum in excellent overall yield.

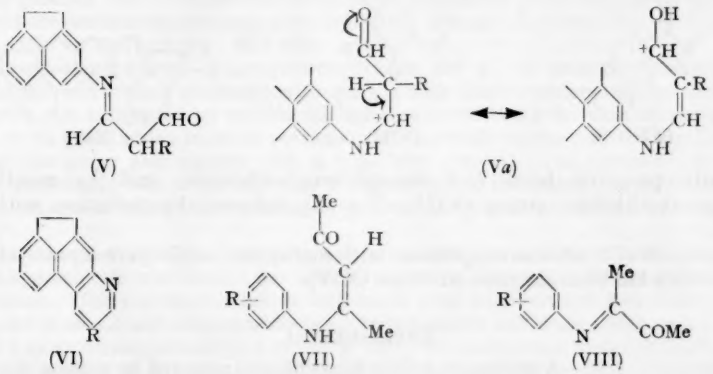
2-Aminoacenaphthene failed to undergo the Skraup reaction as modified by Cohn (*loc. cit.*). Its conversion into the pyrido(2′ : 3′-2 : 3)acenaphthene system (VI), which bears a formal resemblance to 1 : 2-dihydroergotine, was ultimately achieved in disappointing overall yields by adapting the method of Uhle and Jacobs (*J. Org. Chem.*, 1945, **10**, 76) for converting 3-aminonaphthastyril into (±)-dihydrolysergic acid.

Reaction of 2-aminoacenaphthene with cyanomalondialdehyde furnished 2-cyano-3-2′-acenaphthenyliminopropanal (V; R = CN) in *ca.* 20% yield. Similar reaction with nitromalondialdehyde gave the 2-nitro-derivative (V; R = NO_2), but in only 5% yield.

Ring closure of (V; R = CN) by fusion with zinc chloride, followed by hydrolysis (cf. Uhle and Jacobs, *loc. cit.*), furnished a 20% yield of a gelatinous amorphous product which failed to crystallise. Its constitution as (VI; R = CO_2H) was nevertheless established by esterification with methanolic hydrochloric acid, the methyl ester (VI; R = CO_2Me) being crystalline. The low yield of product obtained in the cyclisation undoubtedly arose from the *trans*-configuration of the anil (V; R = CN) [see de Gaouck and Le Fèvre (*J.*, 1938, 741; 1939, 1392; Petrow, *loc. cit.*)] which must undergo thermal isomerisation to a *cis*-structure before ring closure. In accordance with this view we find that conversion of (V) into (VI) is facilitated by removing the steric factors inhibiting ring closure by (*a*) adding a proton to the azomethine link: $-\overset{\curvearrowleft}{N}{=}\overset{*}{C}H- \xrightarrow{H^+} -NH-\overset{+}{C}N-$ and (*b*) reducing the azomethine bond.

This concept of proton addition to the azomethine *N*-atom finds support in the work of Roberts and Taylor (*ibid.*, 1927, 1832; cf. Coombes, *Bull. Soc. chim.*, 1888, **49**, 90; *Compt. rend.*, 1887, **106**, 124) who studied the conversion of certain substituted anils of acetylacetone into the quinolines by brief heating with concentrated sulphuric acid. Their results led

them to assign the *cis*-anilino-structure (VII) to anils undergoing ring closure under these conditions, reserving the anil structure (VIII) for those compounds in which only hydrolysis to the components took place. This explanation, however, can no longer be regarded as adequate. We now find that the infra-red absorption spectra of *o*-, *m*-, and *p*-chloro-anils of acetylacetone (of which only the *m*-isomer yields the quinoline base with concentrated sulphuric acid) have similar absorption bands at 6·2 μ characteristic of the azomethine link but fail to show bands at 6·5, 7·6, and 7·8 μ characteristic of the (chloro)-anilino-group. All three compounds must consequently be assigned structures of type (VIII). Their differing behaviour to concentrated sulphuric acid is thus unlikely to reside in structural differences represented by (VII) and (VIII) but it is readily explained by differences in electron-availability at the N atom. Conversion of (V) into (VI) *via* the resonating cation (V*a*) may consequently be regarded as a special case of the general reaction mechanism for quinoline formation previously proposed by Morley and Simpson (*J.*, 1948, 2024).



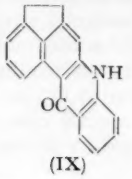
In accordance with (*a*) above we find that brief reaction of (V; R = CN) with hot concentrated sulphuric acid leads to the amide (VI; R = $CO{\cdot}NH_2$) in *ca.* 50% yield. By extending the time of heating, the corresponding acid (VI; R = CO_2H) is obtained in similar yield and may be characterised by conversion into the methyl and the ethyl ester. Syrupy phosphoric acid–phosphoric oxide at 100° may also be employed to convert the nitrile into the amide but the yield in this case is only 30%. The nitro-compound (V; R = NO_2), in contrast, fails to cyclise under these experimental conditions, probably owing to the lower electron-availability at the methine-N atom due to the $+I$ effect of the proximate nitro-group.

An alternative route to (VI) lies in the application of (*b*) (above) in which the nitrile (V; R = CN) and the nitro-compound (V; R = NO_2) are heated with anhydrous formic acid (cf. Hollingsworth and Petrow, *loc. cit.*). Reduction of the methine link accompanied by cyclisation then readily gives the required pyridines in 40% and 20% yield, respectively.

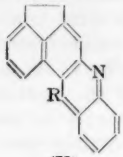
2-Aminoacenaphthene did not condense with *o*-chlorobenzoic acid and copper bronze in amyl alcohol. Results were better in *cyclo*hexanol, a high-melting acidic, presumably impure *N*-2′-acenaphthenylanthranilic acid being obtained in *ca.* 25% yield. In attempts to purify this material through esterification with methanolic hydrochloric acid, a surprisingly ready ring closure gave 1 : 4-dihydro-4-oxo-acenaphtheno(2′ : 3′-2 : 3)quinoline (IX). This afforded the parent (X; R = H) by direct reduction with amalgamated aluminium foil (Albert and Ritchie, *J. Soc. Chem. Ind.*, 1941, **60**, 120) or reaction with phosphorus oxychloride to give 4′-chloro-compound (X; R = Cl), followed by reduction with sodium amalgam.

Reaction of 2-aminoacenaphthene with 2-formyl*cyclo*hexanone gave the Schiff's base, which passed smoothly into the tetrahydro*iso*quinoline (XI) in hot anhydrous formic acid (Hollingsworth and Petrow, *loc. cit.*).

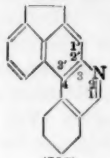
3-Aminoacenaphthene and 2-formyl*cyclo*hexanone gave a Schiff's base, readily converted into the tetrahydroquinoline (XII) by Petrow's method (*loc. cit.*). Its dehydrogenation to the fully aromatic system (XIII; R = H) could not be effected by such reagents as selenium at 260°, sulphur in boiling benzyl benzoate (Simpson, *J.*, 1939, 755), or chloranil in xylene (Barclay and Campbell, *J.*, 1945, 530), or by distillation with lead dioxide (Braun and Gruber, *Ber.*, 1922, **55**, 1710). The base (XIII; R = H) was



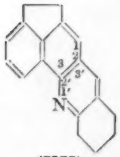
(IX)



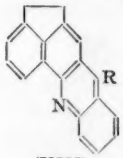
(X)



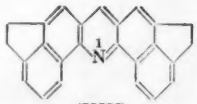
(XI)



(XII)



(XIII)



(XIV)

consequently prepared from *N*-3′-acenaphthenylanthranilic acid by reaction with phosphorus oxychloride, giving (XIII; R = Cl), followed by reduction with sodium amalgam.

Condensation of 3-aminoacenaphthene with methylene iodide gave a pale yellow base, $C_{25}H_{17}N$, which has been assigned structure (XIV).

Experimental

1-*Acenaphthoic Acid.*—A solution of sodium hypochlorite, prepared by passing chlorine at 0° into water (10 ml.) containing sodium hydroxide (3·7 g.) until neutral to litmus, was treated with further sodium hydroxide (0·7 g.) and the mixture added gradually (20 min.) with shaking to a solution of 3-acetylacenaphthene (15 g.) (Fieser and Hershberg, *loc. cit.*) in methanol (40 ml.) at 60°. The mixture was finally heated at 70° for 30 min. and the methanol removed by evaporation. On acidification, 1-acenaphthoic acid was precipitated as an almost pure, white crystalline powder (1·5 g.), m. p. 243°.

The finely powdered acid (1·98 g.) was added gradually to diazomethane (0·8 g.) in dry ether (25 ml.). After 1½ hr. the ether was removed and the product crystallised twice from aqueous ethanol. *Methyl* 1-*acenaphthoate* (1·75 g.) formed pale yellow needles, m. p. 81° (Found: C, 79·5; H, 6·0. $C_{14}H_{12}O_2$ requires C, 79·5; H, 5·7%).

This ester (1·0 g.) and 90% hydrazine hydrate (3·0 ml.) were refluxed together for 6½ hr. On cooling, 1-*acenaphthoylhydrazine* (0·8 g.) separated as colourless plates, m. p. 178° (from ethanol) (Found: C, 73·3; H, 5·9. $C_{13}H_{12}ON_2$ requires C, 73·5; H, 5·7%).

s-*Di*-1-*acenaphthenylurea.*—The hydrazide (0·5 g.), dissolved in warm dioxan (7 ml.), was added, with vigorous shaking, to 2N-hydrochloric acid (13 ml.) and ice (12 g.). To the resulting fine suspension, a solution of sodium nitrite (0·2 g.) in a little water was added dropwise during 30 min. The resulting solid was collected and heated to 100° with 2N-hydrochloric acid (25 ml.) for 10 min. The mixture was filtered, and the residue washed with water. No basic material could be isolated from the washings, but after two crystallisations from nitrobenzene the residue gave s-*di*-1-*acenaphthenylurea*, m. p. 280° (Found: C, 82·4; H, 5·5; N, 7·4. $C_{25}H_{20}ON_2$ requires C, 82·4; H, 5·5; N, 7·7%).

1-*Acenaphthazide.*—1-Acenaphthoyl chloride (1·0 g., prepared by Fieser and Hershberg's method, *loc. cit.*) in dry acetone (25 ml.) was treated at 10° during 5 min. with a solution of sodium azide (1·3 g.) in water (6 ml.). After 30 min., dilution with ice-water (35 ml.) precipitated a pale solid (0·85 g.). After crystallisation from aqueous acetone 1-*acenaphthazide* (0·7 g.) formed yellow needles, m. p. 104° (Found: C, 70·1; H, 4·0; N, 18·6. $C_{13}H_9ON_3$ requires C, 70·0; H, 4·1; N, 18·8%).

The azide (0·65 g.) in benzene (6·5 ml.) was refluxed for 3 hr. Concentrated hydrochloric acid (5 ml.) was then added and heating continued for a further 1½ hr. Water (100 ml.) was added, the benzene layer removed, and the aqueous layer extracted with two 25-ml. portions of ether, which were combined with the benzene. Basifying the aqueous layer alkaline with potassium hydroxide precipitated a light brown solid (0·15 g.) which was identified as 1-aminoacenaphthene by benzoylation to 1-benzamidoacenaphthene, pale yellow needles, m. p. and mixed m. p. 207°. The benzene–ether solution was washed with water, dried and evaporated. The residue crystallised from nitrobenzene as light brown plates of *s*-di-1-acenaphthenylurea, m. p. 280°, not depressed on admixture with a specimen obtained as above.

1-*Acetylacenaphthene oxime*, prepared from 1-acetylacenaphthene (5 g.) in ethanol (30 ml.) and hydroxylamine hydrochloride (2·5 g.), sodium acetate (5·0 g.), and water (10 ml.) under reflux for 2 hr., separated (5·0 g.) in white needles, m. p. 149—150° (Found : C, 79·5; H, 6·3; N, 6·6. $C_{14}H_{13}ON$ requires C, 79·5; H, 6·2; N, 6·5%).

Beckmann Rearrangement of the Oxime.—The foregoing compound (1·0 g.) in dry ether (35 ml.) was treated gradually, with shaking, with phosphorus pentachloride (1·5 g.), a yellow gum separating. The ether was evaporated and the residue decomposed with ice-water. The semi-solid product, on crystallisation from aqueous ethanol (charcoal), gave felted needles (0·4 g.) of 1-acetamidoacenaphthene, m. p. 191—192° (Found : C, 79·3; H, 6·1; N, 6·6. Calc. for $C_{14}H_{13}ON$: C, 79·5; H, 6·2; N, 6·6%).

1-*Acetamidoacenaphthene.*—1-Acetylacenaphthene (20 g.) in molten trichloroacetic acid (100 g.) at 60° was treated gradually with stirring with finely powdered sodium azide (10 g.). The reaction was completed by heating the mixture at 65° for 1 hr. with occasional stirring. Water (150 ml.) was added in small portions with thorough mixing and the resultant magma filtered at the pump and washed with a little 50% ethanol. The product (18 g.) formed yellowish needles and was sufficiently pure for hydrolysis to the amine. A portion crystallised from 50% ethanol as white felted needles, m. p. 192° (Morgan and Harrison, *loc. cit.*, give m. p. 192—193°).

1-*Aminoacenaphthene.*—The foregoing compound (18 g.) in ethanol (500 ml.) and concentrated hydrochloric acid (25 ml.) was refluxed for 12 hr., after which the ethanol was removed by distillation. The residue was boiled with water (500 ml.), concentrated hydrochloric acid (50 ml.), and charcoal, and filtered while hot. When cooled and made ammoniacal, the filtrate deposited 1-aminoacenaphthene (11·0 g.; m. p. 75°). Crystallisation from light petroleum gave nearly white needles, m. p. and mixed m. p. 82° (lit., m. p. 81·5°).

N-1′-*Acenaphthenylanthranilic Acid* (II).—*o*-Chlorobenzoic acid (3·15 g.) in amyl alcohol (15 ml.) was boiled with anhydrous potassium carbonate (2·75 g.) for 1 min. (to expel water and carbon dioxide). 1-Aminoacenaphthene (3·4 g.) and copper bronze (0·2 g.) were added and the mixture heated under reflux in an oil-bath for 4 hr. The amyl alcohol was removed in steam, and the residue dissolved in boiling water (250 ml.; charcoal) and filtered hot. Acidification gave N-1′-*acenaphthenylanthranilic acid* (2·65 g.), m. p. 241° (Found : C, 78·7; H, 5·1; N, 4·8. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2; N, 4·9%), needles from ethanol.

Cyclisation of N-1′-*Acenaphthenylanthranilic Acid.*—The acid (3·0 g.) and phosphorus oxychloride (25 ml.) were refluxed for 1 hr. Chloroform (250 ml.) was added and the solution poured in a thin stream into a well-stirred mixture of concentrated aqueous ammonia and crushed ice. The lower layer was separated, washed with water, and dried ($CaCl_2$), and the solvent was removed. The residue (1·0 g.) crystallised from ethanol to give 1-[*acenaphtheno*-(1′ : 2′-2 : 3)-4-*quinolyl*]-4-*chloroacenaphtheno*(1′ : 2′-2 : 3)*quinolinium chloride* (IV), dark red needles, m. p. 192° (Found : C, 78·5; H, 4·4; Cl, 12·1. $C_{19}H_{12}NCl$ requires C, 78·7; H, 4·2; Cl, 12·3%).

Acenaphtheno(1′ : 2′-2 : 3)*quinoline* (III; R = H).—The foregoing compound (1·0 g.) was finely ground with zinc dust (2·0 g.), and the powder distilled at 15 mm. A dark red oil distilled and was extracted with benzene (15 ml.). The combined benzene extracts from two such distillations were filtered and chromatographed on alumina (40 g.) (Brockman, Grade 1 alumina used throughout). Elution with benzene containing 1% of methanol gave two bands. The first, a narrow yellow band, was rejected. The second, eluted with 50 ml. of the above solvent, formed a broad red band and on evaporation gave an orange-red solid which crystallised from benzene or ethanol, forming red prisms (8 mg.) of *acenaphtheno*(1′ : 2′-2 : 3)*quinoline*, m. p. 153° (Found : C, 89·2; H, 5·2; N, 5·6. $C_{19}H_{13}N$ requires C, 89·4; H, 5·1; N, 5·5%).

3-*Toluene*-p-*sulphonamidoacenaphthene.*—3-Aminoacenaphthene (4·7 g.) in dry pyridine (50 ml.) was cooled in ice and toluene-*p*-sulphonyl chloride (5·4 g.) added with stirring during 5 min. The mixture was set aside for 16 hr. and then poured on ice and concentrated hydro-

chloric acid (50 ml.). The precipitate was collected and crystallised from ethanol giving the *toluenesulphonamide* in grey needles (Found: N, 4·4. $C_{19}H_{17}O_2NS$ requires N, 4·3%).

2-*Nitro*-3-*toluene*-p-*sulphonamidoacenaphthene*.—Finely ground 3-toluene-*p*-sulphonamidoacenaphthene (4·6 g.) in acetic acid (30 ml.) at 0—10° was treated gradually with concentrated nitric acid (14 ml.). After 1 hr. the yellow precipitate was collected and crystallised from ethanol. 2-*Nitro*-3-*toluene*-p-*sulphonamidoacenaphthene* (1·8 g.) formed yellow needles, m. p. 180° (Found: C, 61·8; H, 4·1. $C_{19}H_{16}O_4N_2S$ requires C, 61·9; H, 4·3%).

2-*Nitroacenaphthene*.—3-Amino-2-nitroacenaphthene (9·0 g.) in glacial acetic acid (90 ml.) and concentrated sulphuric acid (45 ml.) was treated slowly at room temperature with finely powdered sodium nitrite (9·0 g.). The mixture was set aside for 1 hr. and then added during 30 min. to a vigorously stirred suspension of freshly prepared cuprous oxide (18 g.) in methanol (350 ml.) at 60°. Nitrogen was evolved and an orange solution formed. Water (1 l.) was added and the resultant precipitate filtered off and washed with sodium carbonate solution and then with water. Extraction of the crude product with ethanol, followed by concentration of the extract, furnished 2-*nitroacenaphthene* (5·3 g.) as golden-yellow needles, m. p. 129° (Found: C, 72·3; H, 4·4; N, 7·0. $C_{12}H_9O_2N$ requires C, 72·4; H, 4·5; N, 7·0%) after one recrystallisation.

2-*Aminoacenaphthene*.—2-Nitroacenaphthene (10·0 g.), ethyl acetate (200 ml.), and platinum oxide (1 g.) were shaken in hydrogen at 20°/2 atm. until absorption was complete. The catalyst was removed and the solvent evaporated. The dark residue was dissolved in benzene (25 ml.) and percolated through alumina (10 g.), the column being washed with a further 10 ml. of benzene. The combined eluates were evaporated to 15 ml. and light petroleum (10 ml.; b. p. 60—80°) added, 2-aminoacenaphthene (7·5 g.) crystallising rapidly as buff-coloured needles, m. p. 87°.

3-2′-*Acenaphthenylimino*-2-*cyanopropanal* (V; R = CN).—Cyanoacetaldehyde diethyl acetal (10·0 g.), ethyl formate (6 g.), and sodium powder (3·0 g.) in dry ether (25 ml.) were left for 16 hr. at room temperature. Ice-water (20 ml.) was added and the aqueous layer, containing the sodium derivative of cyanomalondialdehyde, run dropwise into a well-stirred suspension of finely ground 2-aminoacenaphthene (5 g.) in 2% hydrochloric acid (300 ml.). The dark brown precipitate was collected and triturated with 50% acetone–methanol, and the yellow residue collected and crystallised from ethanol. 3-2′-*Acenaphthenylimino*-2-*cyanopropanal* (2·0 g.) formed yellow needles, m. p. 209° (Found: C, 77·5; H, 5·0. $C_{16}H_{12}ON_2$ requires C, 77·5; H, 4·9%).

Pyrido(2′ : 3′-2 : 3)*acenaphthene*-5′-*carboxyamide* (VI; R = CO·NH_2).—To the foregoing compound (0·3 g.), dissolved in syrupy phosphoric acid (1·0 ml.), phosphoric oxide (2·5 g.) was added with stirring, the temperature rising to 100°. After 1 hr., ice (50 g.) was added together with an excess of aqueous ammonia. The precipitate was collected and crystallised twice from ethanol. The crude amide (0·1 g.) formed yellow needles, m. p. 257°. A small quantity of the carboxylic acid (see below) was isolated from the ammoniacal filtrate by neutralisation.

The *methosulphate*, orange needles (Found: N, 7·6. $C_{18}H_{18}O_5N_2S$ requires N, 7·5%), was prepared by treating the amide (50 mg.) in nitrobenzene (1·0 ml.) with methyl sulphate (0·05 ml.), adding benzene (5 ml.), and washing the precipitate with benzene.

Pyrido(2′ : 3′-2 : 3)*acenaphthene*-3-*carboxylic Acid* (VI; R = CO_2H).—(*a*) The nitrile (V; R = CN) (3·0 g.) and anhydrous, finely ground zinc chloride (1·5 g.) were heated slowly to 250° in an air-bath and this temperature maintained for 10 min. The glass obtained on cooling was ground, extracted 3 times with water, and boiled for 1 hr. with 18% hydrochloric acid (150 ml.), and the mixture filtered. The filtrate was evaporated to dryness *in vacuo* and the residue extracted with an excess of dilute ammonia solution. Neutralisation to litmus gave the acid (VI; R = CO_2H) as a pale yellow gelatinous solid (0·16 g.).

(*b*) The nitrile (0·5 g.) was added gradually with stirring to concentrated sulphuric acid (10 ml.), and the mixture warmed to 100° for 1 hr. Ice (30 g.) was added and the solution made ammoniacal and filtered. Neutralisation of the filtrate gave the acid (0·25 g.).

The crude acid (0·2 g.) was boiled with 3% methanolic hydrochloric acid (5·0 ml.) for 3 hr. On dilution, the *methyl ester* was precipitated. It separated from aqueous methanol in pale yellow needles, m. p. 170° (Found: C, 77·5; H, 4·8; N, 5·1. $C_{17}H_{13}O_2N$ requires C, 77·5; H, 4·9; N, 5·3%). The *ethyl ester*, similarly prepared, formed long yellow needles, m. p. 126° (Found: C, 78·1; H, 5·2. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4%), after crystallisation from ethanol.

3-2-*Acenaphthenylimino*-2-*nitropropanal* (V; R = NO_2).—Mucobromic acid (5 g.) was added in small portions with stirring to a suspension of finely powdered sodium nitrite (5 g.) in water (5 ml.) and ethanol (7 ml.). The mixture was warmed slowly to 50° until effervescence ceased

and then rapidly cooled to −20°. The sodium derivative of nitromalondialdehyde was collected, washed rapidly with ice-cold 50% aqueous ethanol, and dissolved in water (20 ml.). This solution was added dropwise with stirring to a suspension of finely ground 2-aminoacenaphthene (3·0 g.) in 1·5% hydrochloric acid (200 ml.). The resulting dark brown precipitate was crystallised once from ethanol and twice from 60% acetic acid. The *product* (0·4 g.) formed yellow needles, m. p. 210° (Found: C, 67·0; H, 4·3; N, 10·3. $C_{15}H_{12}O_3N_2$ requires C, 67·2; H, 4·5; N, 10·4%).

5'-Cyanopyrido(2' : 3'-2 : 3)*acenaphthene* (VI; R = CN).—The nitrile (V; R = CN) (0·1 g.) and anhydrous formic acid (2·0 ml.) were heated under reflux for 10 hr., then the mixture was poured on ice and aqueous ammonia. The precipitate was collected and crystallised from dilute ethanol. The *product* (15 mg.) formed brownish squat needles, m. p. 201° (Found: C, 83·4; H, 4·5. $C_{16}H_{10}N_2$ requires C, 83·5; H, 4·5%).

5'-Nitropyrido(2' : 3'-2 : 3)*acenaphthene* (VI; R = NO_2), prepared by heating the nitrile (V; R = NO_2) (0·75 g.) with anhydrous formic acid (6·0 ml.) under reflux for 17 hr., formed orange-yellow needles, m. p. 191° (Found: C, 71·6; H, 3·9; N, 11·4. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0; N, 11·2%), after crystallisation from ethyl acetate.

1 : 4-*Dihydro*-4-*oxoacenaphtheno*(2' : 3'-2 : 3)*quinoline* (IX).—2-Aminoacenaphthene (1·7 g.), *o*-chlorobenzoic acid (1·6 g.), anhydrous potassium carbonate (1·5 g.), *cyclo*hexanol (10 ml.), and copper bronze (0·1 g.) were heated under reflux in an oil-bath for 3 hr. The *cyclo*hexanol was removed in steam, and the dark residue extracted with boiling 2N-sodium carbonate (150 ml.) and filtered hot. On acidification, crude *N*-2'-acenaphthenylanthranilic acid (0·75 g.) was obtained, which could not be recrystallised.

This product was dissolved in 10 ml. of ethanol saturated with hydrogen chloride and the solution heated under reflux for 1 hr. The yellow crystalline solid which separated on cooling was collected, boiled with dilute ethanolic sodium hydroxide to remove acidic material and esters, and crystallised from ethanol. The *quinoline* (0·25 g.) formed cream-coloured plates which sublimed, without melting, at 310° (Found: C, 83·9; H, 4·7. $C_{19}H_{13}ON$ requires C, 84·1; H, 4·7%).

4-*Chloroacenaphtheno*(2' : 3'-2 : 3)*quinoline* (X; R = Cl).—The foregoing compound (0·2 g.) and phosphorus oxychloride (1·0 ml.) were heated under reflux for 1 hr., giving the *chloro*-derivative (0·15 g.) as orange-yellow needles, m. p. 171° (Found: C, 4·8; Cl, 12·2. $C_{19}H_{12}NCl$ requires N, 4·9; Cl, 12·3%).

Acenaphtheno(2' : 3'-2 : 3)*quinoline* (X; R = H).—(*a*) The foregoing compound (0·2 g.), 4% sodium amalgam (10 g.), ethanol (20 ml.), and water (10 ml.) were heated under reflux for 2 hr. The mercury was separated, the alcohol removed *in vacuo*, and the residue extracted with benzene (5 ml.). The benzene extract was percolated through a short column of alumina (5 g.), which was washed with a further 10 ml. of benzene. The combined eluates were evaporated to dryness under reduced pressure and the residue crystallised from dilute ethanol. *Acenaphtheno*(2' : 3'-2 : 3)*quinoline* (0·09 g.) formed yellow needles, m. p. 188° (Found: N, 5·5. $C_{19}H_{13}N$ requires N, 5·5%).

(*b*) 1 : 4-Dihydro-4-oxoacenaphtheno(2' : 3'-2 : 3)quinoline (50 mg.) in ethanol (5 ml.) containing amalgamated aluminium foil (0·5 g.) was refluxed for 2 hr. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with benzene (10 ml.), the extract evaporated to dryness, and the residue crystallised from dilute ethanol. The base (15 mg.) formed yellow needles, m. p. 188°, not depressed on admixture with a sample prepared as under (*a*).

2-(2-*Oxocyclohexylmethyleneamino*)*acenaphthene*.—Prepared from 2-aminoacenaphthene by Hollingsworth and Petrow's method (*loc. cit.*) this *compound* formed pale yellow needles, m. p. 229° (Found: N, 4·7. $C_{19}H_{19}ON$ requires N, 5·0%), after purification from ethanol.

5 : 6 : 7 : 8-*Tetrahydroacenaphtheno*(2' : 3'-3 : 4)iso*quinoline* (XI).—The foregoing derivative (1·75 g.) and anhydrous formic acid (15 ml.) were heated under reflux for 24 hr., then the bulk of the formic acid was removed by distillation *in vacuo*. The residue was poured on ice (10 g.) and concentrated aqueous ammonia (5 ml.), and the solids were collected. The product was dissolved in ethanol (10 ml.), and a solution of picric acid (2 g.) in hot ethanol (5 ml.) added. After 16 hr. the precipitated picrate was collected and the base regenerated by shaking it in benzene (20 ml.) with 10% lithium hydroxide solution. The benzene layer was washed with water and evaporated to dryness. The residual iso*quinoline* crystallised from aqueous ethanol in light orange needles, m. p. 162° (Found: C, 88·1; H, 6·7; N, 5·5. $C_{19}H_{17}N$ requires C, 88·0; H, 6·6; N, 5·4%).

5 : 6 : 7 : 8-*Tetrahydroacenaphtheno*(2' : 3'-2 : 3)*quinoline* (XII).—3-(2'-Oxo*cyclo*hexyl-

methyleneamino)acenaphthene (5·5 g.; Hollingsworth and Petrow, *loc. cit.*), 3-aminoacenaphthene hydrochloride (3·4 g.), fused zinc chloride (2·6 g.), and absolute ethanol (100 ml.) were refluxed for 28 hr. During the first 9 hr. red crystals slowly separated, which later dissolved. The mixture was cooled and filtered. The residue was warmed for 10 min. with an excess of 2N-sodium hydroxide, cooled, and filtered. After two crystallisations from ethanol, the residue gave the *quinoline* (2·7 g.) as orange needles, m. p. 136° (Found: C, 88·2; H, 6·7; N, 5·6. $C_{19}H_{17}N$ requires C, 88·0; H, 6·6; N, 5·4%). The product fluoresced an intense blue in ultra-violet light.

4-Chloroacenaphtheno(2′ : 3′-2 : 3)quinoline (XIII; R = Cl).—*N-3′-Acenaphthenylanthranilic acid* formed (36%) golden-yellow plates, m. p. 234° (Found: C, 79·0; H, 5·2; N, 4·9. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2; N, 4·9%). It (7·65 g.) and phosphorus oxychloride (50 ml.) were refluxed for 1 hr. The mixture was cooled, chloroform (250 ml.) added, and the solution poured in a thin stream into a well-stirred mixture of ice and aqueous ammonia (*d* 0·88). The chloroform layer was separated, washed with water, dried ($CaCl_2$), and evaporated to dryness. The orange residue was crystallised twice from ethanol containing a trace of ammonia. The *product* (5·5 g.) formed pale yellow needles, m. p. 183° (Found: C, 78·8; H, 4·4; N, 4·9. $C_{19}H_{12}NCl$ requires C, 78·8; H, 4·2; N, 4·9%).

Acenaphtheno(3′ : 2′-2 : 3)quinoline (XIII; R = H).—The foregoing compound (4·1 g.) in 90% aqueous ethanol (380 ml.) containing 4% sodium amalgam (125 g.) was refluxed for 16 hr., then the mercury was removed and the ethanolic solution concentrated to 200 ml. On cooling, the *base* separated. After two crystallisations from ethanol it formed silky yellow needles (2·15 g.), m. p. 166° (Found: C, 89·2; H, 5·4; N, 5·8. $C_{19}H_{13}N$ requires C, 89·4; H, 5·1; N, 5·8%). The *picrate* formed small needles, m. p. 268° (Found: N, 11·2. $C_{19}H_{13}N,C_6H_3O_7N_3$ requires N, 11·5%), after crystallisation from ethanol.

Diacenaphtheno(3′ : 2′-2 : 3)(2″ : 3″-5 : 6)pyridine (XIV).—To 3-aminoacenaphthene (10·2 g.) at 130°, methylene iodide (8·9 g.) was added. The temperature was raised slowly to 135°, whereupon a vigorous reaction took place. The temperature of the bath was finally raised to 170° for 15 min. The cooled residue was extracted with boiling ethanol (350 ml.) containing potassium hydroxide (1·0 g.), and the extracts were diluted with water (400 ml.). The brown precipitate (8·0 g.) was collected and crystallised three times from boiling pyridine. The *product* (2·4 g.) formed small pale yellow prisms, m. p. 298° (decomp.) (Found: C, 91·0; H, 5·0; N, 4·5. $C_{25}H_{17}N$ requires C, 90·6; H, 5·1; N, 4·3%) (cf. Morgan and Harrison, *J. Soc. Chem. Ind.*, 1930, **49**, 419T).

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Liquid Metals. Part I. The Surface Tension of Liquid Sodium: the Vertical-plate Technique.

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This paper describes the determination of the surface tension of liquid sodium in an atmosphere of pure argon, from measurements on plates of zinc, copper, and molybdenum suspended, and partly immersed, in liquid sodium. In the temperature range 100—200° zinc can be fully wetted by sodium, but copper and molybdenum are not wetted; the technique employed for contact angles of 0° and 180° is described. The surface tension is found to be 195 dynes/cm. at the melting point, and the temperature coefficent is 0·1 dyne/cm./degree.

The study of surface properties in liquid-metal systems is rendered difficult by the ready formation of contaminating films on the metal surface. With the liquid alkali metals, considerable precautions are necessary to prevent the formation of oxide films, and in consequence the earlier values reported for the surface tension of liquid sodium show a wide scatter. The first determination (252 dynes/cm. at the melting point) was made by Quincke (*Ann. Physik*, 1868, **135**, 621) using the drop-weight method and an atmosphere of carbon dioxide. Poindexter and Kernaghan (*Phys. Review*, 1929, **33**, 834) measured a sessile drop of sodium in a vacuum, and obtained a value of 206·4 dynes/cm. at 103°. By use of the capillary-rise technique, values in the range 110—125 dynes/cm. have been reported ("Liquid Metals Handbook," 2nd Edn., NAVEXOS P-733, Rev., p. 53, U.S. Govt. Printing Office, Washington D.C., 1952) but the fact that the value varied with the material used to contain the sodium illustrates the unsatisfactory nature of the results.

The main objective of the present work is the study of the wetting of solid metals by liquid metals, and the influence on contact angles of such factors as temperature, atomic structure of the metal, physical state of the surface, and oxide films. The technique now described was originally designed for contact-angle measurements; a plate of the solid metal is partly immersed in the liquid metal, and the force on the plate is dependent upon (*inter alia*) the surface tension of the liquid metal and the contact angle. A knowledge of the surface tension is therefore essential for contact-angle measurements; however, by suitable selection of the solid metal it has been possible to define conditions under which the contact angle is either 0° or 180°, and the apparatus may then be used for the measurement of surface tensions of liquid metals.

Experimental

Vertical-plate Apparatus.—The apparatus is shown diagrammatically in Figs. 1*a* and 1*b*. The torsion device was housed in a brass box 25 × 21 × 15 cm. (shown in broken outline in Fig. 1*b*) through which argon was normally circulated *via* openings at *C* and *D*. The whole apparatus could be evacuated if desired. *AB* was a stainless-steel torsion wire 0·0406 cm. in diameter and 18 cm. long, free from fatigue. It was held firmly at *A* and *B* in chucks which were inserted, through lock-nuts, into Wilson seals set into the walls of the box. These seals allowed the chucks to be turned, but prevented ingress of air. *A* was normally maintained in a fixed position, while *B* was attached to the pointer *P* on the outside of the box (Fig. 1*a*). *E* was a light aluminium arm 13 cm. long (V-shaped to prevent bending) which was clamped rigidly to the torsion wire by block *F*. The vertical plate was suspended from the end of arm *E* by nichrome wire (diam. 0·051 cm.); this wire was looped through a hole in the end of arm *E* only slightly greater in diameter than the wire, so that the wire was free to move in a vertical plane. The weight of the arm, the plate, and its suspension wire was approximately counterbalanced by a weight suspended as shown on the opposite side of block *F*. The movement of the vertical plate (and thus arm *E*) was followed by an optical lever system. A concave mirror *M* of long focal length was mounted on *F*, and a spot-light and hair-line were reflected, through the glass window

W, on to a circular scale *S* having its centre at *M*, and of about 1 m. radius. The position of the vertical plate with respect to the liquid sodium surface was controlled by movement of pointer *P*. The characteristics of the torsion wire were such that the movement of *P* through an angle of 180° caused a vertical displacement of the plate (when hanging free) of about 7 cm. Calibration curves from which the force on the plate could be obtained from the setting of pointer *P* and the scale reading were derived as follows. The plate was allowed to hang freely (*i.e.*, in the absence of liquid sodium) and the scale reading corresponding to a particular setting of *P* was noted; a series of known weights were then suspended on the plate, and a force–scale reading graph obtained. This was repeated for a range of pointer settings, the calibration curves being determined when the apparatus was at the temperature at which the tension measurement was to be carried out.

The plate suspension wire passed out of the brass box down the centre of a brass tube 3·2 cm. in diameter, which was attached by a metal vacuum union *G* to the glass system. The vessel *K* in which the plate was suspended carried a B.55 ground-glass joint, and was 10 cm. in diameter. This was sufficiently wide to ensure that when the vessel contained sodium, the plate was immersed in a plane surface, and that the measurements were not influenced by sodium–glass meniscus effects. Vessel *K* carried a side arm in which a micrometer *H* (containing a silicone

FIG. 1*a*.

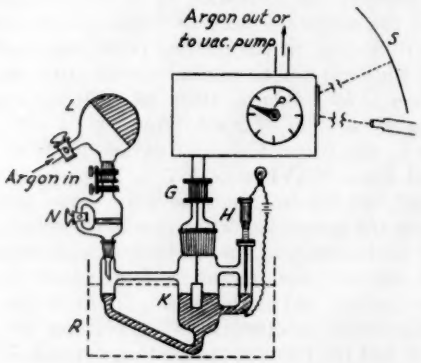
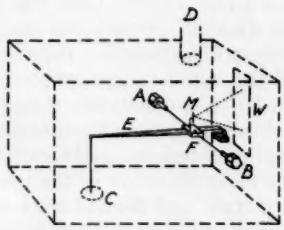


FIG. 1*b*.



rubber vacuum seal) and a probe were attached. This was used to detect any change in the sodium level during an experiment. In conjunction with a cathetometer it could also be used to determine the depth of immersion of the plate, although this depth was more conveniently obtained directly from readings on scale *S*.

Method.—The experiment was carried out as follows. The sodium (which had been given preliminary purification as described below) was contained in vessel *L*; *L* was attached, by a B.24 ground-glass joint, to the filtration unit *N* which contained a Grade 3 sintered-glass plate 7 cm. in diameter. The joint was held by a metal clip in order to withstand the pressure of argon gas necessary during filtration. The filtration unit was connected to vessel *K* through a B.14 joint as shown. The apparatus was first evacuated; vessels *N* and *K* were heated (by Electrothermal heating tapes) to a temperature about 100° above that of the experiment, in order to degas the glass. Purified argon gas was then allowed to flow through the apparatus at a rate of about 1 l./min. The oil thermostat *R* was raised into position, and the filter unit *N* and the vessel *L* were heated to 120° by wrapping them with heating tapes. During this stage the tap *N* was kept open. The sodium in *L* melted, and flowed on to the sintered plate; when 40—50 ml. had collected on the plate, tap *N* was closed, and the sodium forced through the plate into vessel *K* by argon pressure. This process was repeated until *K* contained the necessary quantity of sodium (normally about 150 ml.), whereupon tap *N* was left open and vessel *L* allowed to cool. The plate was lowered until it touched the sodium surface, and the scale reading noted. The procedure followed thereafter depended upon whether the plate was wetted by sodium.

(a) *Zinc plates.* The influence of surface condition of the zinc on rates of wetting will be discussed in a later paper. For plates prepared as described below, wetting was almost immediate. The plate was immersed to a depth of 2—3 cm. and then gradually withdrawn. The

scale readings corresponding to a series of settings of the pointer P were noted, and the corresponding force on the plate used in the calculation of surface tension.

(b) *Copper and molybdenum plates.* Wetting did not occur with these plates within the temperature range employed. The plate was pressed into the surface, and scale readings noted for a series of pointer settings. The depth of immersion of unwetted plates was limited; as soon as the plate was immersed beyond the floating position, it moved to the side of vessel K, preventing further measurement.

Depth of immersion of the plate. This was determined from the scale readings when the plate touched the surface (S_s) and when immersed to depth l (S_l). From the geometry of the apparatus, $l = 0{\cdot}0682(S_l - S_s)$ cm.

Correction for sodium wetting the zinc plate. It was necessary to subtract the weight of the sodium film from the measured force in the suspension wire. This was done by selecting an appropriate pointer setting, and noting the change in scale reading for the freely hanging plate before immersion in, and after removal from, sodium. From this change, the calibration curves gave the weight of sodium wetting the full area of plate which had been immersed. Jeffreys (*Proc. Camb. Phil. Soc.*, 1930, **26**, 204) derived the relation $z^2 = \eta y/gt_1$ between the thickness of film z and the distance y below the wetted edge, for a liquid draining from a vertical surface with zero contact angle; η is the kinematic viscosity and t_1 the time of draining. This equation being applied to the plates used, the weights of sodium wetting the plate are 0·009, 0·007, and 0·005 g. for draining times of 5, 10, and 20 sec., respectively. The equation is based on considerations of liquid flow only, and the direct measurements referred to above showed that the weight of sodium retained was near 0·034 g. in all experiments with plates of standard size. Since drainage times longer than the above were normally used, there remains 0·03 g. of sodium which must be adhering to the plate as an intermetallic compound (*e.g.*, $NaZn_{12}$: Mathewson, *Z. anorg. Chem.*, 1906, **48**, 196). This compound does not dissolve in sodium, and must decompose in water to leave the zinc on the plate, since the weight of the plate after being immersed in sodium and cleaned by washing with water and drying with alcohol and ether, differed from the weight of the original plate by less than 0·001 g. This weight of combined sodium was used as a constant correction, to be added to the weight of the plate irrespective of the immersion depth. This procedure assumes that the dimensions of the plate are not altered by this combined sodium; if this is not so, then a slight correction should also be made to the buoyancy term *txdl* in equation (1) (p. 2864). That this latter correction is unnecessary is indicated by the constancy of the tension values for a range of immersion depths. Again, it has no bearing on the final tension value, since the buoyancy term becomes less significant as the plate is withdrawn from the liquid.

No such corrections were necessary with the copper and molybdenum plates, which showed no change in weight after immersion in sodium.

Preparation of Plates.—The plates measured approximately 5 × 2 × 0·06 cm. Molybdenum plates were abraded with emery paper of grades 1 to 4/0, and then degreased in a Soxhlet extractor with dry acetone for 12 hr. The plate was removed from the acetone, and dried rapidly in a current of warm air, immediately before use in a tension measurement. Some zinc plates were prepared similarly, and some were electropolished in an orthophosphoric acid bath prepared as described by Jacquet (*Métaux Corrosion Usure*, 1944, **19**, 71), a current density of 2·2 amp./sq. dm. and 2·5 volts being used. Copper plates were electropolished in orthophosphoric acid (*d* 1·4) at 2·0 amp./sq. dm. and 2·2 volts, a copper cathode being used.

Density of Sodium.—The values used in calculation were those given by Ewing, Atkinson, and Rice (N.R.L. Report C.3287, 1948) which conform to the equation $d = 0{\cdot}957 - 2{\cdot}7 \times 10^{-4}T$.

Purification of sodium. The sodium used was supplied by British Drug Houses Ltd.; the maximum content of other metals is as follows; Ca, 0·069; Fe, 0·0007; Mn, 0·0001; Ni, 0·00005; Cu, 0·0002; Pb, 0·0003%. The impurity which has the greatest influence on surface properties, and which is most difficult to remove, is oxygen (present as Na_2O). Sodium monoxide has an exceedingly low solubility in liquid sodium. Direct measurements (collected references in "Liquid Metals Handbook," *op. cit.*, p. 114) have shown the solubility to be less than 0·002% over the temperature range used in this work. As an alternative to distillation, Bornemann (*Z. angew. Chem.*, 1922, **35**, 227) has described the removal of oxide by filtration through sintered stainless-steel plates. This gives liquid sodium containing little more than the oxide dissolved at the temperature of filtration. We have found sintered-glass plates to be very successful for oxide removal, and the fact that the surface tension of sodium so purified agrees closely with values determined by Taylor (A.E.R.E. Report M/R 1247, 1953) on carefully distilled sodium supports this. Although sodium metal does not wet glass, sodium monoxide adheres strongly to glass, and the oxide in excess of that dissolved can therefore be removed by bringing liquid

sodium into contact with a sufficient area of glass surface. This was achieved by the passage of sodium through the sintered-glass plate in unit *N* (Fig. 1*a*). The function of this plate was not filtration as normally understood; instead it provides a means of finely subdividing the sodium, and thus bringing it into intimate contact with a large area of glass surface.

The sodium was given a preliminary filtration through glass-wool to remove the main bulk of oxide and carbonate. It was then solidified, cut in an argon-filled dry box, and transferred to a vertical glass tube 4 cm. in diam. and 50 cm. long. This tube carried a constriction near the bottom, on which rested a 5-cm. plug of cleaned glass-wool. Argon was led into the top of the tube, and the round-bottomed flask shown as *L* in Fig. 1*a* was attached at the bottom. The tube was wrapped with heating tapes and warmed to about 100°, and the main proportion of the volatile contaminants carried away in a stream of argon. The temperature was then raised to 150°, the sodium flowing through the glass-wool plug into flask *L*. This flask was then isolated in a stream of argon, attached to a high-vacuum line, and gaseous impurities were removed from the sodium by heating for 5 hr. at 250°/10^{-5} mm. The metal was then allowed to solidify, and the flask transferred to the position shown in Fig. 1*a*. The temperature of final filtration through the plate *N* was kept as low as possible; although the temperature coefficient of solubility of sodium monoxide is small at temperatures up to 250°, it was observed in early experiments that low values of tension resulted when the sodium was filtered at a temperature above that used for the tension measurement.

Purification of Argon.—Argon of the highest purity was necessary to prevent surface contamination of the sodium. The argon used (British Oxygen Co. Ltd.) was 99·8% pure. This was further purified by passage through fresh calcium metal chips heated to 700°, and then through stainless-steel bubblers containing sodium–potassium alloy.

Results and discussion

When a metal plate is suspended and partly immersed in liquid sodium, the equilibrium state is expressed by the equation

$$\gamma \cos \theta = g[txdl + (F - W)]/2(t + x) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where γ is the surface tension of sodium, θ is the contact angle, t, x, and W are the thickness, width, and weight of the plate, l is the depth of immersion of the plate, d is the density of sodium, and F is the force (in grams weight) exerted by the suspension wire. This relation

Table 1.

Surface age of sodium = 110 min. Electropolished zinc plate. Temp. = 176°. "Wetted plate" correction = 0·030 g.

t = 0·051 cm. x = 2·06 cm. W = 2·861 g. d = 0·910 g./c.c. S_s = +3·55.

Pointer setting	S_l	Immersion depth, l cm.	$txdl$ (g.)	$F - W$ (g.)	$\gamma \cos \theta$ (dynes/cm.)
80°	40·3	2·51	0·240	0·405	143
90	37·5	2·38	0·203	0·593	182
100	27·6	1·64	0·157	0·678	187
110	17·1	0·94	0·090	0·752	188
115	10·3	0·46	0·044	0·783	185
120	4·5	0·06	0·006	0·825	186

Table 2

Expt. No.	Dynes/cm.	Metal plate	Expt. No.	Dynes/cm.	Metal plate	Expt. No.	Dynes/cm.	Metal plate
1	186	Abraded zinc	6	187	Abraded zinc	11	186	Electropolished zinc
2	185	,,	7	186	,,	12	189	,,
3	185	,,	8	186	,,	13	187	Copper
4	186	,,	9	186	,,	(170°)		
5	187	,,	10	183	Electropolished zinc	14	186	Molybdenum

may be employed to determine either γ or θ provided that the other is known. The manner in which $\gamma \cos \theta$ varies as the depth of immersion of a zinc plate is decreased is shown in Fig. 2; γ is constant, and the initial rapid increase in $\gamma \cos \theta$ reflects the decrease in receding

contact angle. When θ reaches 0° the curve changes direction, and thereafter $\gamma \cos \theta$ ($= \gamma$) is constant. With copper and molybdenum plates, the value of $-\gamma \cos \theta$ increases rapidly as the plate is forced into the surface. When the advancing angle θ reaches 180° the curve changes direction sharply, and $-\gamma \cos \theta$ ($= \gamma$) is constant throughout further immersion of the plate. The detailed results of one typical experiment are given in Table 1, in order to illustrate the relative magnitude of the terms in equation (1).

A series of such determinations has been carried out and Table 2 gives the γ values obtained at or near 180°. Errors in measurement are considered to lead to an experimental error of ± 1 dyne/cm., and the results are therefore reported to the nearest dyne. The mean of these values gives the surface tension of sodium as 186 dynes/cm. at 180°.

Temperature Coefficient of Tension.—By using an abraded zinc plate, values of the surface tension have been determined over the temperature range 128—180°, and are shown in Fig. 3. A number of metals show a " critical wetting temperature " above which wetting by sodium is a ready process, but below which wetting occurs with difficulty, if at all. This property will form the subject of a later paper, but it is relevant that the critical wetting temperature for zinc falls within the temperature range used. When the zinc plate was immersed in sodium at 128°, the contact angle remained large and the tension

FIG. 2.

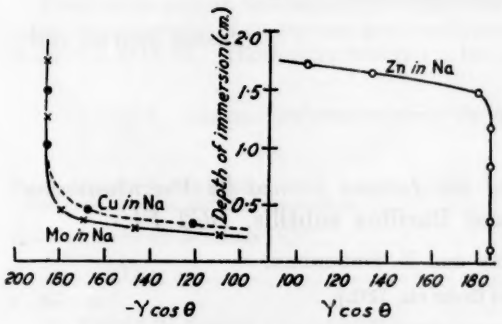
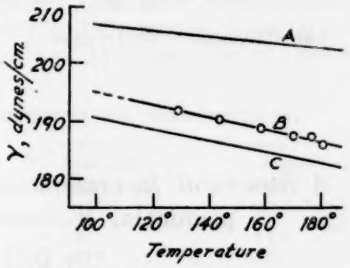


FIG. 3.



A, from results of Poindexter and Kernaghan (*loc. cit.*)
B, present work.
C, from results of Taylor (*loc. cit.*).

could not be determined. However, when the plate was wetted at 180°, and the sodium then cooled below the critical wetting temperature, the contact angle remained at zero; this technique was used where necessary in obtaining the tension values shown in Fig. 3. The temperature coefficient is $-0{\cdot}1$ dyne/cm. degree^{-1}, and extrapolation gives $\gamma = 195$ dynes/cm. at the m. p. of sodium. These results are in quite good agreement with values recently obtained by Taylor (*loc. cit.*) using the maximum bubble pressure method; the temperature coefficient is in each case the same, and is in good agreement with a value $-0{\cdot}09$ dyne/cm. degree^{-1} calculated by Skapski (*J. Chem. Phys.*, 1948, **16**, 386).

Influence of Surface Films of Sodium Oxide.—Taylor (*loc. cit.*) finds $\gamma = 191$ dynes/cm. at the m. p.; a difference of 4 dynes/cm. is not, in fact, likely to represent any real disagreement in view of the corrections necessary in the two widely different techniques. In Taylor's measurements great care was also taken to avoid contamination of the sodium surface by oxide, but since there is always the possibility, with strongly electropositive metals, that slight contamination may occur, it is necessary to consider the influence of oxide films on surface tension. The surface tension of fused metal oxides is normally much lower than that of the corresponding liquid metals (see Bondi, *Chem. Rev.*, 1953, **52**, 417). Consistently with this, sodium oxides are not wetted by liquid sodium, since the condition $\gamma_{solid} > \gamma_{liquid}$ is desirable before wetting takes place. Provided that the oxide content of the metal is below the solubility limit, its presence in the surface will almost certainly lower the tension of the liquid metal. When sufficient oxide is present at the surface to form an insoluble film, the effect on tension depends upon the cohesive nature of the oxide concerned.

Sodium oxide films are strongly cohesive, and increase the apparent surface tension. In measurements on sodium using the drop-weight method, apparent values of surface tension as high as 300 dynes/cm. were observed when the drops carried a visible film of oxide. Therefore the effect of sodium oxide at the surface is first to lower the tension, and then to increase it. There appears to be no justification, however, for the assumption that the higher tension values reported by Poindexter and Kernaghan (*loc. cit.*), and shown in Fig. 3, arise from oxide contamination of the sessile drop, although the temperature coefficient, 0·05 dyne/cm. degree^{-1}, is unusually low for a metallic element. These measurements were carried out in a high vacuum, and may well represent the true surface tension of sodium under these conditions. It is well known (*e.g.*, with mercury) that the presence of adsorbed gases or vapours can lower the surface tension of liquid metals.

Variation of Surface Tension with Time.—The measurements referred to in Table 2 were normally continued for periods of 2—3 hr. In many cases no change in tension took place during this time. Occasionally, a slight fall in tension occurred after one hour, but this did not exceed 2 dynes/cm. The slight decrease is attributed to oxide contamination, since argon flowed over the metal surface throughout the experiment.

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A Structural Re-examination of the Levans formed by Pseudomonas prunicola, *Wormald, and* Bacillus subtilis, *BG2 F1.*

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Both micro-organisms, grown on sucrose as the main source of carbon, produce levans of high molecular weight, presumably by *trans*-fructosidation. Both fructosans are shown to comprise highly branched molecules. The predominant linkage is that of the typical levan (2 : 6′) while the branching linkage is (2 : 1″) (" inulin type "). The anomeric form of the glycosidic link is assumed to be β, from rotational and enzymic evidence.

LEVANS may be defined as fructosans in which the 2β : 6′-inter-radical linkage predominates, while inulins may be likewise considered to be those fructosans in which 2β : 1′-links unite the major fraction of the molecule. Levans of small molecular weight, unbranched or of very low degrees of branching, are found in quantity in the aerial portions of the Gramineae (Laidlaw and Reid, *J.*, 1951, 1830; Bell and Palmer, *J.*, 1952, 8763; Aspinall, Hirst, Percival, and Telfer, *J.*, 1953, 337; Schlubach and his collaborators, numerous papers in *Annalen*). Levans of large molecular weight are formed, exocellularly, by enzymes (" levansucrases "; Hestrin and Aveneri-Shapiro, *Biochem. J.*, 1944, **38**, 2) secreted by spore-forming aerobes such as *Bacillus subtilis, B. mesentericus*, and *B. megatherium.* The predominant inter-radical link in these fructosans is 2β : 6′, as was first shown by Hibbert and his co-workers (cf. Evans and Hibbert, *Adv. Carbohydrate Chem.*, 1946, **2**, 204) by the isolation and characterisation of 1 : 3 : 4-tri-*O*-methyl-D-fructose. This sugar was obtained from *B. subtilis* levan in over 98·5% yield. If this sugar was in fact uncontaminated it would indicate the possibility that levans handled by Hibbert and his colleagues were long-chain, and possibly unbranched, polysaccharides. Challinor, Haworth, and Hirst (*J.*, 1934, 676), using fractional distillation of the methanolysis products of methylated levan (*B. mesentericus*), estimated a chain length of 10—12 units. Some uncharacterised dimethyl-

fructose was detected in these experiments, which could be taken to indicate a highly branched structure. Lyne, Peat, and Stacey, by the same procedure, deduced similar chain lengths for levans from *B. megatherium*, *Phytomonas pruni*, and *Pseudomonas prunicola* (*J.*, 1940, 237).

Palmer (*Biochem. J.*, 1951, **48**, 389), using D-glucose oxidase, detected about one D-glucose molecule in 500 derived by hydrolysis of levan from *B. subtilis* (a different strain from that in the present work.) Hydrolysed levan from *Ps. prunicola*, Wormald contained no glucose detectable by the enzyme. It is possible that the *prunicola* levan either was so large that glucose liberated on hydrolysis is swamped by the accompanying fructose molecules, or had lost its glucose radical by enzyme action during isolation or before. That the bacterial levans might be derived by chain-lengthening transfer of β-fructofuranosyl (or β-fructofuranosido) radicals from a donor molecule to an acceptor, *ab initio* sucrose, would account for the presence of a glucose moiety as a molecular component. Such a process of biological synthesis seems very likely in the instances of the plant levans and inulin.

Confirmation of this speculation has been afforded by Dedonder and Noblesse (*Ann. Inst. Pasteur*, 1953, **85**, 356) who showed the formation of an ascending series of D-glucose-containing oligosaccharides during enzymic synthesis of levan by the levan sucrase of the strain of *B. subtilis* used in the present work.

Using silica column chromatography (Bell and Palmer, *J.*, 1949, 2522) we have investigated the structures of two levans produced respectively by *Ps. prunicola*, Wormald, and *B. subtilis* BG2 F1. The former material is the sample used by Palmer (*loc. cit.*) and by

TABLE 1. *Summarised comparison of the two levans and their trimethyl ethers.*

	Levan of *Ps. prunicola*	Levan of *B. subtilis*
Purified levan: $[\alpha]_D$ in H_2O	−71°	−54°
Presence of D-glucose after hydrolysis	Negative	Negative
Trimethyl levan sol. in dioxan (%)	100	14 *
OMe (%)	45·6	—
$[\alpha]_D$ in $CHCl_3$	−63°	—
Hydrolysate		
(*a*) Paper qual. analysis: sugars found	Fructose Me_4, Me_3, and Me_2 ethers	Fructose Me_4, Me_3, and Me_2 ethers
(*b*) Silica column quant. analysis and identification; sugars found: molar ratios		
D-Fructose 1 : 3 : 4 : 6-Me_4 ether	1	—
,, 1 : 3 : 4-Me_3 ,,	7—8	—
,, 3 : 4-Me_2 ,,	1	—
Trimethyl levan insol. in dioxan (%)	0	86
OMe (%)	—	45·2
$[\alpha]_D$ in $CHCl_3$	—	−58°
Hydrolysate		
(*a*) Paper qual. analysis: sugars found	—	Fructose Me_4, Me_3, and Me_2 ethers
(*b*) Silica column quant. analysis and identification; sugars found: molar ratios		
D-Fructose 1 : 3 : 4 : 6-Me_4 ether	—	1
,, 1 : 3 : 4-Me_3 ,,	—	7—8
,, 3 : 4-Me_2 ,,	—	1

* The total material soluble in dioxan was obtained as " Fractions I and III " (see Experimental section).

Beattie and Bell (*Quart. J. Physiol.*, 1953, **38**, 1); the strain of the latter organism is that, from the collection of Mlle. Delaporte, used by Dedonder and Noblesse (*loc. cit.*). Beattie and Bell, examining the excretion of certain fructosans by the dog kidney, concluded that *prunicola* levan has a very high molecular size. *B. subtilis* levan is likewise of large size since the bulk of it can be centrifuged down at 25,000 **g**; work is in progress (at the Institut Pasteur) to determine its molecular weight.

Neither of the hydrolysates of these levans contained D-glucose detectable by paper chromatography. The use of D-glucose oxidase, however, showed the presence of D-glucose radicals in very small relative proportions.

Using the procedure of Bell and Palmer (*J.*, 1949, *loc. cit.*), Murphy (*Canad. J. Chem.*, 1952, **30**, 872) analysed the hydrolysis products of the methylated levan of *B. polymyxa* and obtained 1 : 3 : 4 : 6-tetra-, 1 : 3 : 4-tri-, and 3 : 4-di-*O*-methyl-D-fructoses in the ratios of 1 : 4 : 0·66. From the author's description of his fractions we conclude that they may not have been completely pure; none the less, traces of impurities would not affect his conclusion that this polysaccharide is very highly branched, and that the unit-chain length is considerably shorter than that of other bacterial fructosans.

As will be seen from Table 1, the " average chain " structures of both of our highly branched molecules are not to be distinguished by our chemical methods. However, the specific rotations, in water, of the two levans are markedly different, as are the solubilities in dioxan of their methylated derivatives, but we are unable yet to explain these differences.

Since methylation of both levans is accompanied by some losses (~6% per treatment) we feel justified in claiming only that the bulk of their molecules are composed of unit-chains having average lengths of 9—10 radicals. This is rather shorter than that deduced from the earlier analyses noted above which, however, were carried out by fractional distillation and when the characterisation of fructose derivatives had not reached its present efficiency. Since the silica-column chromatogram yields sharply defined fractions with no overlap we feel justified in believing that our results are not inaccurate. We draw attention to the fact that we have isolated both terminal radicals (tetramethyl fructose) and branch-point radicals (dimethylfructose) in homogeneous and equimolar amounts. The di-*O*-methyl-D-fructose is the 3 : 4-derivative, indicating that the linkage between the 2 : 6′-linked chains is of the inulin type and may be described as 2 : 1″. So far no bacterial fructosan has been found containing proved linkages other than 2 : 6′ or 2 : 1″, and there is no evidence that these are other than β in configuration.

Experimental

Evaporation of solvents was done below 40°. Optical rotations were measured in a 2-dm. tube.

Isolation of the Levans.—(*a*) The levan from *Ps. prunicola* (Wormald) was the preparation made, and used, by Beattie and Bell (*loc. cit.*). It had $[\alpha]_D$ −54° in H_2O.

(*b*) The medium (Grelet, *Ann. Inst. Pasteur*, 1951, **81**, 43; with sucrose 6 g./100 ml.) in which the *B. subtilis* was grown was first cleared of bacteria and solid debris by passage through a Sharples centrifuge. The resulting fluid was treated first with barium acetate at pH 8·2, filtered, and then saturated with barium hydroxide. The levan–barium complex was decomposed by carbon dioxide, and the fructosan isolated by freeze-drying (Beattie and Bell, *loc. cit.*). It had $[\alpha]_D$ −71° in H_2O and contained 0·3% of nitrogen.

Hydrolysis of the Levans.—This was done by heating solutions in 0·02N-sulphuric acid for 30 min. on the boiling-water bath. The recovery of fructose (colorimetric determination) was 96—97%.

Search for D-Glucose in the Hydrolysates.—(a) *By paper chromatography.* *n*-Butanol–ethanol–water (4 : 1·1 : 1·9) (Dedonder, *Bull. Soc. chim.*, 1952, **19**, 874) being used as solvent, portions (2 cu. mm.) of hydrolysates corresponding to 5, 10, and 20% solutions of the levans, after development, showed no detectable amounts of aldose when sprayed with aniline hydrogen phthalate.

(b) *By D-glucose oxidase* (cf. Palmer, *loc. cit.*). Data are given in Table 2. We consider that no significance can be attached to results obtained with D-glucose oxidase when the concentration of D-glucose is below 1 millimole in presence of 500 millimoles of other hexoses.

Table 2. *Examination of levan hydrolysates with D-glucose oxidase.*

Substrates	*Ps. prunicola* levan hydrolysate		*B. subtilis* levan hydrolysate		D-Fructose control	D-Glucose control
Amount of hexose examined (millimoles)	494	494	500	500	500	5
O_2 consumed (millimoles)	0	0·25	0·15	0	0	2·5
D-Glucose assayed from O_2 consumed	0	0·5	0·3	0	0	5
Moles of D-glucose per 100 moles of D-fructose	0	0·1	0·06	0	0	1

Methylation of the Levans.—The polysaccharides were treated with methyl sulphate and 30% (w/v) sodium hydroxide in presence of dioxan, and the products purified, as described by Bell and Palmer (*J.*, 1952, 3763) for grass levans.

(a) *Prunicola* levan (8·8 g., dry/wt.), after two methylations, was completely soluble in dioxan. The product, obtained by distilling off the dioxan in presence of an excess of water, amounted to 8·5 g. (86·2%; mean loss per methylation treatment, 6·7%). $[\alpha]_D$ was −63° in $CHCl_3$ (Found: OMe, 45·6%).

(b) *Subtilis* levan. The levan (4·0 g.) was methylated three times. The product was only partly soluble in dioxan (500 ml.). The insoluble material was separated on a glass filter bearing a layer of Celite; concentration of the filtrate to small bulk, followed by hot-water precipitation, yielded fraction I (174 mg.; 4% of final total). The residual solid was dissolved in chloroform (500 ml.), and the solution washed with an equal volume of water and then dried (Na_2SO_4). Light petroleum (b. p. 40—60°; 800 ml.) was added till no more precipitate formed. The resulting product (fraction II) weighed 3·80 g. (86% of final total) and had $[\alpha]_D$ −58° in $CHCl_3$ (Found: OMe, 45·2%). The chloroform–light petroleum mother-liquor was evaporated; the residue was soluble in dioxan from which water precipitated fraction III (425 mg.; 10% of final total).

The total yield of material accounted for was 4·4 g. (87·5%; mean loss per methylation treatment, 4·1%).

Paper-chromatographic Examination of the Methylated Levan Hydrolysates.—Samples of the methylated levans were hydrolysed by the method used for quantitative analysis. [Fractions I, II, and III from *B. subtilis* were examined separately. With aqueous butanol for development, each hydrolysate showed the presence of tetra-, tri-, and di-methylhexuloses (urea–HCl spray).] With aniline hydrogen phthalate spray no aldose derivatives were found.

TABLE 3. *Quantitative analysis of the hydrolysed methylated levans.*

Source of material	*Ps. prunicola*	*B. subtilis*
Wt. hydrolysed (mg.)	2566	1988
Total wt. of fractions recovered from column (mg.)	2530	1915
Recovery (%)	90·5	88·7
1 : 3 : 4 : 6-Tetra-*O*-methyl-D-fructose fraction:		
Wt. (mg.)	275	225
OMe (%) (distilled material)	52·1	52·1
$[\alpha]_D^{20}$ (H_2O) ,, ,,	+28°	+30°
n_D^{20} ,, ,,	1·4506	1·4502
Purity of fraction by oxidation with alkaline 3 : 5-dinitrosalicylate (%) [a]	100	100
Ketose spots detected on paper chromatography	Me_4 only	Me_4 only
Molar ratio	1	1
1 : 3 : 4-Tri-*O*-methyl-D-fructose fraction (crystalline):		
Wt. (mg.)	1922	1512
OMe (%)	—	41·0
$[\alpha]_D^{20}$ (H_2O)	−56·3°	−55·8°
n_D^{20}	1·4666	1·4665
CH_2O from IO_4^- oxidation [b] (mol.)	0·98, 0·96	0·97
Ketose spots detected on paper chromatography	(*a*) Me_3 (*b*) ?Me_2 trace *	Me_3
Molar ratio	7—8	7—8
3 : 4-Di-*O*-methyl-D-fructose fraction:		
Wt. (mg.)	263	178
OMe (%)	29·6	29·6
$[\alpha]_D^{20}$ (H_2O)	−50·9°	−60·6°
n_D^{20}	1·4843	1·4855
CH_2O from IO_4^- oxidation [b]	1·51	1·63
Phenylosazone, m. p.	—	127—128°
Mixture with 3 : 4-di-*O*-methyl-D-glucosazone, m. p.	—	127—128°
Ketose spots detected on paper chromatography	(i) Me_2 (ii) trace of faster-moving material *	Me_2
Molar ratio	1	1

* These traces may be due to a tetramethyldifructose dianhydride formed by autocondensation of two molecules of 3 : 4-di-*O*-methylfructose (Bell, unpublished work).

[a] Bell, Manners and Palmer, *J.*, 1952, 3760. [b] Bell, Palmer, and Johns, *J.*, 1949, 1537.

Quantitative Analysis of the Hydrolysis Products.—By Bell and Palmer's procedure (*J.*, 1949,

2522), hydrolysates of the methylated levans (fraction II from *B. subtilis* only) were analysed on 15-g. columns of silica. The results are summarised in Table 3.

Paper Chromatography. Differentiation of Certain Methylated Fructoses by Alkaline Triphenyltetrazolium Spray.—Sprayed with an alkaline triphenyltetrazolium solution (cf. Wallenfels, *Naturwiss.*, 1950, **37**, **491**; Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, **444**) and kept at 50° for 45 min. in an atmosphere with water vapour, papers bearing spots of the methylated fructoses noted provide a simple means of differentiating between 3 : 4-dimethyl- and 3 : 4 : 6-trimethyl-fructose on the one hand (red spots) and 1 : 3 : 4-trimethyl- and 1 : 3 : 4 : 6-tetramethyl-fructose on the other (no reaction with reagent).

When a paper chromatogram of the crystalline trimethylfructose fraction from *prunicola* levan was treated as above, a red colour appeared on the most advanced edge of the sugar spot. This indicated the contamination of the 1 : 3 : 4-tri-*O*-methylfructose by a reducing isomer. The fraction was therefore crystallised from carbon tetrachloride; the contaminant was found to be concentrated in the mother-liquor. Dr. D. H. Northcote kindly examined the material isolated from the carbon tetrachloride, by borate-paper electrophoresis (Consden and Stanier, *Nature*, 1952, **169**, 783). From Table 4 it will be noted that the substance is very probably

TABLE 4. *Paper-electrophoretic examination of trimethylfructose contaminant in boric acid, with* 3 : 4 : 6-*tri*-O-*methyl*-D-*glucose as standard.*

Sugar	Presence or absence of vicinal (*cis*)-OH groups	Electrophoretic displacement from start-line
2 : 4 : 6-Tri-*O*-methylglucose	Absent	0
1 : 3 : 4-Tri-*O*-methylfructose	,,	0
3 : 4 : 6-Tri-*O*-methylglucose	Present	1·0 (Marker)
3 : 4 : 6-Tri-*O*-methylmannose	,,	1·45
3 : 4 : 6-Tri-*O*-methylfructose	,,	2·4
Contaminant	?	2·4

3 : 4 : 6-tri-*O*-methylfructose. No attempt was made to assay the amount of this contaminant; its origin is obscure. It appeared, from spray reaction, to be a hexulose derivative.

One of us (R. D.) is grateful to the British Council and to the Centre National de la Recherche Scientifique for grants which enabled him to carry out part of this work at Cambridge.

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*Amino-acids and Peptides. Part XII.** α- *and* β-L-*Aspartyl*-L-*valine.*

By W. D. JOHN and G. T. YOUNG.

[Reprint Order No. 5308.]

Benzyloxycarbonyl-L-aspartic anhydride has been shown to be dimorphous. With L-valine methyl ester it gave α- and β-coupling products, from which α- and β-L-aspartyl-L-valine have been obtained in the usual way. Unexpectedly, the α-dipeptide yields 1 mol. of carbon dioxide on prolonged heating with ninhydrin. There is also an indication, from paper chromatography, that when heated for some hours in aqueous solution it is partly converted into the β-isomer.

IN Part VI (Le Quesne and Young, *J.*, 1952, 24) it was shown that benzyloxycarbonyl-L-aspartic anhydride reacts with amino-esters to give both α- and β-aspartyl derivatives, which were separated by fractional extraction from an organic solvent with aqueous sodium carbonate. This method has now been used to prepare α- and β-L-aspartyl-L-valine.

In Part VI (*loc. cit.*) we recorded a melting point of 111° for benzyloxycarbonyl-L-

* Part XI, *J.*, 1954, 662.

aspartic anhydride, for which Bergmann, Zervas, and Salzmann (*Ber.*, 1933, **66**, 1288) gave a melting point of 124°. We have now shown that this compound is dimorphous, and in contact with organic solvents the lower-melting slowly changes into the higher-melting form.

Coupling of the anhydride with L-valine methyl ester was effected both in anhydrous ethyl acetate and in the presence of aqueous sodium hydrogen carbonate. In both cases nearly quantitative yields of the mixed products were obtained, and in view of the economy with the ester the latter method was used subsequently. The isomers so formed were separated by fractional extraction from ethyl acetate with small portions of aqueous sodium carbonate (Le Quesne and Young, *J.*, 1950, 1954). Repeated fractionation gave crystalline benzyloxycarbonyl-α- and -β-L-aspartyl-L-valine methyl esters, which were hydrolysed to the acids; hydrogenation gave α- and β-L-aspartyl-L-valine. Paper chromatography revealed only one component in each case, the isomers being well separated when a mixture of *n*-butanol, acetic acid, and water was used as the mobile phase.

We remarked in Part VI (*loc. cit.*) on the characteristic blue colour given with ninhydrin by the β-aspartyl-peptides described there. This was observed on paper chromatograms, and is given by β-L-aspartyl-L-valine also. However, when aqueous solutions of the β-peptides are heated with ninhydrin, in the presence of sodium acetate, a red-brown colour is obtained, and a similar colour is given under Moore and Stein's conditions (*J. Biol. Chem.*, 1948, **176**, 367); asparagine behaves similarly. α-Aspartyl-peptides give the usual purple colour with ninhydrin on paper, and blue with Moore and Stein's solution.

We have determined the carbon dioxide evolved when the dipeptides react with ninhydrin under the conditions of Van Slyke, Dillon, MacFadyen, and Hamilton (*ibid.*, 1941, **141**, 627). The β-aspartyl-peptide, having a free α-amino-carboxyl group, gave 1·0—1·1 mols. of carbon dioxide (at pH 2·5). α-Aspartyl-peptides have only a β-amino-carboxyl group, but α-L-aspartyl-L-valine evolved appreciable amounts of carbon dioxide in 7 min.; when heating was continued for 20 min., *ca.* 1 mol. of carbon dioxide was obtained. No aspartic acid or valine (or β-dipeptide, see below) could be detected by chromatography on paper of a solution of the dipeptide which had been heated similarly, without the addition of ninhydrin. Although β-alanine evolves 0·16 mol. of carbon dioxide after 6 minutes' heating at pH 4·7, none is evolved at pH 2·5 (*idem, loc. cit.*).

Le Quesne (Thesis, Oxford, 1950) observed that when aqueous solutions of α-L-aspartyl-L-tyrosine and -L-glutamic acid had been heated for some hours at 100°, the colour given with ninhydrin by the remaining dipeptide on the paper chromatogram was blue, not purple. Similar treatment of solutions in 0·5N-hydrochloric acid resulted only in hydrolysis, and it was suggested that in the former case conversion into the β-isomer had occurred. We have now further indications of such isomerisation in the case of α-L-aspartyl-L-valine. Partition chromatography of an aqueous solution which had been heated for 6 hr. at 100° showed the presence of aspartic acid and valine, and of a substance corresponding in position to β-L-aspartyl-L-valine, and giving a blue colour with ninhydrin. In a similar experiment in the presence of sodium hydrogen carbonate, neither amino-acid nor β-dipeptide was detected, the α-dipeptide apparently remaining unchanged. Chromatography of an aqueous solution of the β-dipeptide which had been heated at 100° for 6 hr. revealed little change. There is some analogy with the rearrangement observed when the ethyl ester of benzoyl-DL-*iso*asparagine is heated with sodium carbonate (Battersby and Robinson, *Chem. and Ind.*, 1954, 45), and we hope to examine the reaction further.

Experimental

Benzyloxycarbonyl-L-aspartic Anhydride.—Finely powdered benzyloxycarbonyl-L-aspartic acid (10·2 g.) was dissolved in acetic anhydride (7 ml.) by warming to 45° with shaking. After 2 hr. the mixture had solidified; the crystals were washed with cold, dry ether and dissolved in hot ether. After removal of some solvent *in vacuo*, light petroleum (b. p. 60—80°) was added, giving colourless needles, m. p. 109—110° (7·3 g., 78%). Recrystallisation from ether–light petroleum gave long needles, m. p. 111°, $[\alpha]_D^{15}$ −38·6° (*c*, 2·25 in glacial acetic acid). In later

preparations, the crude product was dissolved in ether and allowed to crystallise below 0°; prisms were deposited, m. p. 123°, raised to 124° by recrystallisation from ether–light petroleum, $[\alpha]_D^{15}$ −37·3° (*c*, 2·88 in glacial acetic acid) (Found: C, 58·0; H, 4·6; N, 5·2. Calc. for $C_{12}H_{11}O_5N$: C, 57·8; H, 4·5; N, 5·6%). A saturated solution of the higher-melting form in glacial acetic acid at 16° had n_D^{16} 1·3961; a similar solution prepared from a mixture of both forms had n_D^{16} 1·3979 (see Williams and Young, *J.*, 1951, 1745). Infra-red absorption spectra of the two solids were nearly identical.

Benzyloxycarbonyl-α- and -β-aspartyl-L-valine Methyl Esters.—(*a*) L-Valine methyl ester (3·9 g.) in ethyl acetate was added to benzyloxycarbonyl-L-aspartic anhydride (2·0 g.) in ethyl acetate. After 48 hr. at room temperature the acidic products were extracted into aqueous sodium carbonate, from which they were removed after acidification by extraction with ethyl acetate. Removal of the solvent *in vacuo* left a solid mixture of the α- and β-isomers (2·9 g., 95%).

(*b*) L-Valine methyl ester hydrochloride (3·4 g.) and potassium hydrogen carbonate (6 g.) were dissolved in water (45 ml.) under ethyl acetate (30 ml.). Benzyloxycarbonyl-L-aspartic anhydride (5·0 g.) in ethyl acetate (30 ml.) was added, and stirring was continued for 2 hr. at room temperature. Next morning the aqueous layer was separated and acidified and the mixed isomers were extracted with ethyl acetate as before (7·3 g., 95%).

The crude products (27·6 g.) obtained by both methods were fractionated by dissolving them in ethyl acetate and extraction with 10-ml. portions of N-sodium carbonate. Acidification of the extracts gave oils which slowly solidified. Continued refractionation of the early fractions gave *benzyloxycarbonyl-β-L-aspartyl-L-valine methyl ester*, m. p. 160—162° (7·9 g., 27%), raised to 163—164·5° by recrystallisation from ethyl acetate, $[\alpha]_D^{19}$ −13·3° (*c*, 2·20 in H_2O containing 1 equiv. of sodium hydroxide) (Found: C, 56·7; H, 6·4; N, 7·1. $C_{18}H_{24}O_7N_2$ requires C, 56·8; H, 6·4; N, 7·4%).

Refractionation of the middle and later fractions gave *benzyloxycarbonyl-α-L-aspartyl-L-valine methyl ester* (11·7 g., 40%), m. p. 102—104°, $[\alpha]_D^{19}$ −8·4° (*c*, 2·34 in H_2O containing 1 equiv. of sodium hydroxide) (Found: C, 56·5; H, 6·3; N, 7·3%).

Benzyloxycarbonyl-α-L-aspartyl-L-valine.—The corresponding ester was hydrolysed with 2N-sodium hydroxide (2·2 equiv.) at room temperature for 20 min. Acidification gave the *acid* as an oil which crystallised slowly (yield, 90%), m. p. 137—139°, raised to 138—140° by recrystallisation from ethyl acetate–light petroleum. No optical rotation was observed in water containing 1 equiv. of sodium hydroxide (*c*, 2·4) (Found: C, 55·3; H, 6·1; N, 7·6. $C_{17}H_{22}O_7N_2$ requires C, 55·7; H, 6·1; N, 7·6%).

Benzyloxycarbonyl-β-L-aspartyl-L-valine.—The corresponding ester similarly gave the *acid*, m. p. 171—172°, raised to 172—173° by recrystallisation from acetone, $[\alpha]_D^{20}$ −24·8° (*c*, 2·41 in H_2O containing 1 equiv. of sodium hydroxide) (Found: C, 56·0; H, 6·2; N, 7·3%).

α-L-Aspartyl-L-valine.—Hydrogenation of the benzyloxycarbonyl derivative in the presence of palladium black gave the *dipeptide* (yield, quantitative) which, recrystallised from aqueous *n*-propanol, had m. p. 161—164°; $[\alpha]_D^{20}$ 0° ± 1° (*c*, 2·34 in H_2O), $[\alpha]_D^{20}$ +14° (*c*, 2·34 in glacial acetic acid), R_F in phenol 0·35, in *n*-butanol–acetic acid–water (62 : 12 : 26 vol.) 0·46 (Found: C, 44·6; H, 7·1; N, 11·4. $C_9H_{16}O_5N_2,\frac{1}{2}H_2O$ requires C, 44·8; H, 7·1; N, 11·6%). Hydrolysis in 20% hydrochloric acid gave a solution with the expected optical activity.

β-L-Aspartyl-L-valine.—This *dipeptide* was obtained similarly and had m. p. 197—200°, $[\alpha]_D^{20}$ −10° (*c*, 1·48 in H_2O), R_F in phenol 0·39, in *n*-butanol–acetic acid–water (62 : 12 : 26 vol.) 0·33 (Found: C, 44·5; H, 6·9; N, 11·9%).

Decarboxylation of the Dipeptides by Ninhydrin.—Under the conditions of the α-amino-carboxyl determination (Van Slyke *et al.*, *loc. cit.*), β-L-aspartyl-L-valine gave 1·0—1·1 mol. of carbon dioxide in 7 min. at 100° and pH 2·5. When α-L-aspartyl-L-valine was heated similarly for 20 min., *ca.* 1·0 mol. of carbon dioxide was evolved; shorter periods of heating gave smaller and variable amounts of carbon dioxide. In a control experiment, the α-dipeptide was heated similarly for 20 min. but without the addition of ninhydrin; paper chromatography (with phenol and with *n*-butanol–acetic acid–water) failed to reveal aspartic acid, valine, or β-dipeptide in the product.

Effect of Heating Aqueous Solutions of the Dipeptides.—Solutions (1%) of the dipeptides were sealed into test tubes and heated in a boiling-water bath for 6 hr. The resulting solutions were examined by paper chromatography, with phenol and with *n*-butanol–acetic acid–water as solvents. α-L-Aspartyl-L-valine gave spots corresponding in position to aspartic acid, valine, unchanged dipeptide, and β-L-aspartyl-L-valine (blue); known samples were run beside the unknown. β-L-Aspartyl-L-valine, similarly treated, gave chromatograms showing unchanged

dipeptide only. A solution of the α-dipeptide in aqueous sodium hydrogen carbonate was heated at 100° for 6 hr.; the solution was then made acid to Congo-red and a little sodium acetate was added. Chromatography showed the presence of α-dipeptide only, the spot corresponding in position to that obtained from a solution prepared similarly but not heated.

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The Influence of Molecular Shape upon Dielectric Relaxation Times.

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Measurements are recorded of the relaxation times τ at infinite dilution of 32 different solutes, including methyl, *tert.*-butyl, phenyl, diphenylyl, and naphthyl derivatives. Carbon tetrachloride is the solvent most frequently concerned. Correlations between τ and a number of properties of the solute are mentioned; the relationship of τ with mean polarisability multiplied by a " shape factor " is illustrated graphically.

As is well known, Debye's original formula (1) only very roughly forecasts the

$$\tau = 4\pi\eta r^3/kT \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

relaxation time τ of a molecule from the radius r and a coefficient of inner friction η. Practical attention has been given much more to the dependence of τ on η than to τ on r (cf. " Dielectrics," *Trans. Faraday Soc.*, 1946, **42**, *A*, for references and details). However, the model assumed for the derivation of (1), *viz.*, a spherical polar molecule in a homogeneous uniform medium, is obviously too simple. Perrin (*J. Physique*, 1934, **5**, 497) considered an ellipsoid to be a better approximation to reality and replaced r^3 by products of appropriate half-axes; the idea has been further elaborated by Budo, Fischer, and Miyamoto (*Physikal. Z.*, 1939, **40**, 337). For another problem (cf. Barclay and Le Fèvre, *J.*, 1950, 556; Holland and Le Fèvre, *J.*, 1950, 2166; Angyal, Barclay, and Le Fèvre, *J.*, 1950, 3370; Buckingham and Le Fèvre, *J.*, 1952, 1932), the degrees by which molecules depart from spherical symmetry have been represented by " shape factors." It seemed possible that these might be introduced in an empirical amendment or alternative to (1). Accordingly, a preliminary survey has been made of the values of τ of about 30 different species, selected to have extensions along or across the directions of their resultant dipole moments.

EXPERIMENTAL

Measurements have been made on solutions in carbon tetrachloride or benzene, the majority in the former. Power from an oscillator (incorporating a reflex Klystron, type CV-35), operating at 3109 Mc., was fed to an E_{010} cavity resonator. This was made from 4"-diameter brass rod, its depth being 4·5 cm. and internal radius 3·56 cm. It was fitted with a brass lid through the centre of which was a guide-hole (diameter 0·8 cm.). All surfaces were silver-plated. Half-way down the wall were two diametrically opposed holes through which were inserted two silver-plated " magnetic " probes, each fixed in orientation by a counter-sunk screw adjustable from the top of the resonator when the lid (itself held by six screws) was removed. The energy from the oscillator to the resonator and that from the resonator to the detector was controlled by small rotations of the probe loops. The solution to be examined, in a silica tube, stood vertically through the guide-hole in the centre of the resonator lid. Power was taken from the resonator to a detector consisting of a silicon–tungsten rectifier (Sylvania Electric Co.) in series with a galvanometer. The frequency was progressively increased from below to above that for resonance, and the current–frequency curve recorded. As the width of this curve at

half-height, *i.e.*, Δf, was 1—2 Mc., a beat method was employed to obtain Δf: power from the above oscillator was fed into a mixer with power from a similar oscillator adjusted to give a beat frequency within the range 13·5—18·5 Mc. The frequency of the main oscillator was adjusted to the two half-height frequencies in turn, and the beat frequencies were measured. Their difference gave Δf. Since the detector crystal on calibration had been found to follow the "square law," the Q factor of the circuit was $f_{\text{resonance}}/\Delta f$; Q was determined successively for the pure solvent and for the solutions. The incremental loss tangent, $\Delta \tan \delta$, was $A(1/Q_{12} - 1/Q_1)$, where suffix 1 refers to the solvent, 2 to the solute, 12 to the solution, and A is a constant determined by the properties of the resonator.

The computation of τ has been based on the following argument, starting with Debye's equation (2):

$$\Delta \tan \delta = \frac{(\varepsilon_{12} + 2)^2}{\varepsilon_{12}} \cdot \frac{2\pi f\tau}{(1 + 4\pi^2 f^2\tau^2)} \cdot \frac{4\pi\mu^2 N c_2}{27kT} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

in which c_2 is measured in moles of solute per c.c. and other symbols have their usual meanings. Since solutions have been made up by weight, concentrations are conveniently given as weight fractions of solute, w_2. Appropriate transformation of c_2 into w_2 allows (2) to be rewritten as (3):

$$\Delta \tan \delta = (\varepsilon_{12} + 2)^2 w_2 d_{12} K/\varepsilon_{12} M_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $K = 8\pi^2 f\mu^2 N\tau/27kT(1 + 4\pi^2 f^2\tau^2)$ and M_2 is the molecular weight of the solute. It is not necessary to know the dielectric constants and densities of the mixtures used. At the dilutions used in this work ε_{12} and d_{12} may be each taken as rectilinear with w_2. Insertion of $\varepsilon_{12} = \varepsilon_1(1 + \alpha w_2)$ and $d_{12} = d_1(1 + \beta w_2)$ into (3), and differentiation with respect to w_2, etc., gives

$$[\mathrm{d}(\Delta \tan \delta)/\mathrm{d}w_2]_{w_2=0} = Kd_1(\varepsilon_1 + 2)^2/M_2\varepsilon_1 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The left-hand side of (4) can be obtained from experiment (either by calculating the "line of best fit" of $\Delta \tan \delta$ against w_2, or as the mean $\Sigma(\Delta \tan \delta)/\Sigma w_2$); calling it ϕ, we have ultimately (since f is always *ca.* 3·109 × 10^9 cycles/sec.):

$$\tau = \frac{5{\cdot}1993 \times 10^{28} D\mu^2}{M_2 T\phi} \pm \left[\frac{2{\cdot}7032 \times 10^{57} D^2\mu^4}{M_2^2 T^2\phi^2} - 2{\cdot}6204 \times 10^{-21}\right]^{\frac{1}{2}} \quad . \quad . \quad (5)$$

D in (5) is $d_1(\varepsilon_1 + 2)^2/\varepsilon_1$; around room temperature it has the following values for the two solvents now used:

T, °K	ε	d	D	T, °K	ε	d	D
	Carbon tetrachloride				*Benzene*		
295	2·2323	1·5900	12·758	295	2·2784	0·8770	7·046
293	2·2360	1·5940	12·792	293	2·2825	0·8791	$7{\cdot}063_5$
291	2·2398	1·5979	12·824	291	2·2866	0·8812	7·081
289	2·2435	1·6019	12·857	289	2·2905	0·8834	7·100
288	2·2454	1·6039	12·874	288	2·2925	0·8844	7·108

The various solutes had the m. p.s or b. p.s recorded for pure specimens in Beilstein's "Handbuch." Methyl chloride and bromide were prepared and dissolved as indicated respectively by Barclay and Le Fèvre (*loc. cit.*) and Buckingham and Le Fèvre (*J.*, 1953, 3432).

Essential observations are recorded in Table 1; sub-headings give, in order, solute, solvent, and temperature. The variations in Q for $w_2 = 0$ shown in Table 1 are due to the fact that the value of Q of the resonator system seemed to be dependent upon the state of polish of the internal surfaces of the cavity: Q was greatest immediately after silvering and decreased with age. Measurements were not taken chronologically in the order shown. However, the value of $\Delta \tan \delta$, derived from the differences of the values of $1/Q$ for a given solution and its solvent, is independent of the actual magnitude of $1/Q_1$, since $1/Q_{12}$ and $1/Q_1$ are equally affected.

Results, calculated by eqn. (5), are set out in Table 2. Experience, gained by repetitions and redeterminations at different dates, suggests that the smaller relaxation times (τ) may vary by about ±15% and the larger (those over 10 × 10^{-12} sec.) by ±10%; these ranges are indicated by the diameters of the circles surrounding the points on the Figure.

Three of these solute–solvent systems have been examined by other authors, who report values of τ not differing seriously from those now found (see Table 3).

TABLE 1. *Dependence of incremental* tan δ *on concentration.*

$10^5 w_2$	Δf (Mc.)	$10^4/Q_{12}$	$10^3(\Delta \tan \delta)$
Methyl chloride, carbon tetrachloride, 20°			
0	0·71	2·28	—
922	1·17	3·76	1·83
971	1·18	3·80	1·87
1184	1·28	4·12	2·27
Methyl bromide, carbon tetrachloride, 22°			
0	1·28	4·12	—
370	1·34	4·31	0·236
494	1·36	4·37	0·310
864	1·52	4·89	0·955
0	0·94	3·02	—
859	1·11	3·57	0·682
0	0·91	2·93	—
1866	1·28	4·12	1·48
Methyl iodide, carbon tetrachloride, 22°			
0	0·94	2·99	—
5970	1·82	5·85	3·55
8930	2·24	7·20	5·23
Nitromethane, carbon tetrachloride, 22°			
0	0·77	2·48	—
187	1·17	3·76	1·59
236	1·27	4·08	1·98
Acetonitrile, carbon tetrachloride, 22°			
0	1·26	4·05	—
366	2·48	7·98	4·87
485	2·90	9·33	6·55
Toluene, carbon tetrachloride, 22°			
0	0·82	2·64	—
2883	0·93	2·99	0·43
4774	1·00	3·22	0·72
7205	1·09	3·51	1·08
Fluorobenzene, carbon tetrachloride, 14°			
0	1·16	3·73	—
1156	1·74	5·60	2·32
1458	1·90	6·11	2·95
1602	2·00	6·43	3·35
1729	2·09	6·72	3·71
1853	2·04	6·56	3·51
Chlorobenzene, carbon tetrachloride, 14°			
0	1·23	3·96	—
379	1·54	4·95	1·23
737	1·78	5·73	2·20
1493	2·51	8·07	5·10
Bromobenzene, carbon tetrachloride, 24°			
0	1·20	3·86	—
2131	2·70	8·68	5·98
4271	4·26	13·70	12·20
Iodobenzene, carbon tetrachloride, 14°			
0	1·18	3·80	—
988	1·69	5·44	2·04
0	1·30	4·18	—
1497	2·22	7·14	3·67
1806	2·33	7·50	4·12
Benzonitrile, carbon tetrachloride, 14°			
0	1·19	3·83	—
86	2·10	6·75	3·62
317	4·86	15·63	13·96
400	6·14	19·75	19·07
417	6·25	20·10	19·50
788	10·09	32·45	34·82
0	1·36	4·37	—
926	10·50	33·77	36·46
Nitrobenzene, benzene, 20°			
0	2·02 *	6·50 *	—
145	2·34 *	7·53 *	1·67
290	2·61 *	8·39 *	3·06
1344	5·39 *	17·33 *	17·54
0	1·10	3·54	—
292	2·11	6·79	4·03
553	2·86	9·20	7·02
721	3·45	11·10	9·37
o-*Xylene, carbon tetrachloride, 14°*			
0	1·13	3·63	—
2465	1·39	4·47	1·04
8097	2·01	6·47	3·52
8299	1·97	6·34	3·36
m-*Xylene, carbon tetrachloride, 14°*			
0	1·29	4·15	—
9839	1·56	5·02	1·08
9970	1·57	5·05	1·12
16,138	1·81	5·82	2·07
18,980	1·83	5·89	2·16
4-*Chlorodiphenyl, benzene, 20°*			
0	1·16	3·73	—
666	1·57	5·05	1·64
1657	2·25	7·24	4·35
0	1·14	3·67	—
614	1·54	4·95	1·59
4-*Nitrodiphenyl, benzene, 22°*			
0	1·07	3·44	—
272	2·32	7·47	5·05
369	2·89	9·30	7·26
0	1·02	3·28	—
257	2·29	7·37	5·07
317	2·59	8·33	6·26
α-*Nitronaphthalene, carbon tetrachloride, 20°*			
0	1·22	3·92	—
116	1·95	6·27	2·91
0	1·25	4·02	—
217	2·62	8·43	5·47
α-*Nitronaphthalene, benzene, 15°*			
0	1·22	3·93	—
68	$1{\cdot}42_5$	4·58	0·81
225	1·95	6·27	2·90
320	2·24	7·22	4·08
p-*Chloronitrobenzene, carbon tetrachloride, 20°*			
0	1·23	3·96	—
418	2·72	8·75	5·94
433	2·74	8·81	6·02
p-*Nitrotoluene, benzene, 22°*			
0	0·95	3·06	—
147	1·80	5·78	3·37
0	1·15	3·70	—
231	2·50	8·04	5·38
tert.-*Butyl chloride, carbon tetrachloride, 24°*			
0	0·81	2·61	—
670	1·22	3·92	1·64
1020	1·50	4·83	2·75
1483	1·80	5·79	3·95
2067	2·12	6·82	5·23
2394	2·33	7·49	6·06

* The quartz tube in these observations was different from that used for all the others now reported.

TABLE 1. (*Continued.*)

10^5w_2	Δf (Mc.)	$10^4/Q_{12}$	$10^3(\Delta \tan \delta)$
tert.-Butyl bromide, carbon tetrachloride, 20°			
0	1·01	3·25	—
570	1·34	4·31	1·31
1957	2·12	6·82	4·43
tert.-Butyl iodide, carbon tetrachloride, 20°			
0	0·78	2·51	—
567	1·07	3·44	1·16
1734	1·62	5·21	3·35
2048	1·90	6·11	4·47
2651	2·20	7·08	5·66
α-Fluoronaphthalene, carbon tetrachloride, 14°			
0	1·10	3·54	—
561	1·58	5·08	1·91
1728	1·93	6·21	3·31
β-Fluoronaphthalene, carbon tetrachloride, 15°			
0	1·14	3·67	—
747	1·89	6·08	2·99
1413	2·54	8·17	5·58
α-Chloronaphthalene, carbon tetrachloride, 20°			
0	1·10	3·54	—
271	1·33	4·28	0·92
1724	2·60	8·36	5·98
2005	2·79	8·97	6·73
β-Chloronaphthalene, carbon tetrachloride, 12°			
0	1·05	3·38	—
322	1·46	4·70	1·64
634	1·84	5·92	3·15

10^5w_2	Δf (Mc.)	$10^4/Q_{12}$	$10^3(\Delta \tan \delta)$
α-Bromonaphthalene, carbon tetrachloride, 12°			
0	1·06	3·41	—
737	1·65	5·31	2·36
981	1·81	5·82	2·99
β-Bromonaphthalene, carbon tetrachloride, 14°			
0	1·27	4·08	—
172	1·43	4·60	0·65
305	1·55	4·99	0·77
0	1·16	3·73	—
311	1·45	4·66	1·15
α-Iodonaphthalene, carbon tetrachloride, 12°			
0	1·03	3·31	—
1161	1·71	5·50	2·72
0	1·06	3·40	—
1595	2·00	6·43	3·76
0	1·15	3·70	—
2338	2·51	8·07	5·42
β-Iodonaphthalene, carbon tetrachloride, 12°			
0	1·06	3·40	—
276	1·27	4·08	0·84
706	1·58	5·08	2·08
Camphor, benzene, 15°			
0	1·11	3·57	—
1201	2·66	8·56	6·19
0	1·19	3·83	—
1768	3·58	11·52	9·53
2203	4·06	13·07	11·46

TABLE 2. *Calculation of relaxation times.*

Solute	ψ	Temp.	M_2	μ, D	$10^{12}\tau$, sec.
CH_3Cl	0·192	22°	50·5	1·79	1·8
CH_3Br	0·082	20	94·9$_5$	1·70	1·8
CH_3I	0·059	22	142	1·48	2·5
$CH_3{\cdot}NO_2$	0·84	22	61	3·14	3·1
$CH_3{\cdot}CN$	1·35	22	41	3·38	2·8
$C_6H_5{\cdot}CH_3$	0·015	22	92	0·35	6·7
C_6H_5F	0·203	14	96·5	1·44	5·4
C_6H_5Cl	0·33	14	112·6	1·58	8·6
C_6H_5Br	0·285	24	157	1·51	12
C_6H_5I	0·23	14	204	1·39	15
$C_6H_5{\cdot}CN$	4·25	14	103	4·02	17
$C_6H_5{\cdot}NO_2$	1·30	20	123	3·95	11 *
o-Xylene	0·041	14	106	0·53	9·0
m-Xylene	0·012	14	106	0·26	11
$4\text{-}C_6H_4Ph{\cdot}Cl$	0·26	20	189	1·56	32 *
$4\text{-}C_6H_4Ph{\cdot}NO_2$	1·97	22	199	4·17	35 *

Solute	ψ	Temp.	M_2	μ, D	$10^{12}\tau$, sec.
$1\text{-}C_{10}H_7{\cdot}NO_2$	2·52	20°	173	3·88	19
,,	1·28	15	173	3·88	17 *
$p\text{-}ClC_6H_4{\cdot}NO_2$	1·40	20	157	2·6	25
$p\text{-}CH_3{\cdot}C_6H_4{\cdot}NO_2$	2·31	22	137	4·44	19 *
CMe_3Cl	0·253	24	92·5	2·14	3·0
CMe_3Br	0·226	20	137	2·19	3·7$_5$
CMe_3I	0·214	20	184	2·14	5·0
$\alpha\text{-}C_{10}H_7F$	0·30	14	146	1·35	15
β- ,,	0·40	15	146	1·43	18
$\alpha\text{-}C_{10}H_7Cl$	0·34	14	163	1·42	18
β- ,,	0·50	12	163	1·62	20
$\alpha\text{-}C_{10}H_7Br$	0·31	12	207	1·41	21
β- ,,	0·37	14	207	1·55	21
$\alpha\text{-}C_{10}H_7I$	0·232	12	254	1·32	23·5
β- ,,	0·30	12	254	1·42	27
Camphor	0·52	15	152	2·94	9·7 *

* Determined in benzene.

TABLE 3. *Previous determinations relevant to Table 2.*

Solute	Solvent	$10^{12}\tau$, sec.	Source
CMe_3Cl	CCl_4	3·4	Curtis, McGeer, Rathmann, and Smyth, *J. Amer. Chem. Soc.*, 1952, **74**, 644
Camphor	C_6H_6	9·5	Whiffen, *Trans. Faraday Soc.*, 1950, **46**, 130
$C_6H_5{\cdot}NO_2$	C_6H_6	12·0	Spengler, *Physikal. Z.*, 1941, **42**, 134
,,	,,	11·6	Jackson and Powles, *Trans. Faraday Soc.*, 1946, **42**, *A*, 106
,,	,,	13·0	Cripwell and Sutherland, *ibid.*, p. 151
,,	,,	11·5	Whiffen and Thomson, *ibid.*, p. 118
,,	,,	12·8	Whiffen, *loc. cit.*
,,	,,	12·7	Curtis *et al.*, *loc. cit.*

Discussion

The results illustrate the general tendency for τ to increase with increasing molecular size or weight. Such behaviour has been noted before, particularly for certain homologous series (cf. Böttcher, "Theory of Dielectric Polarisation," Elsevier Publ. Co., 1952, Chap. 10, for references). Table 2, however, shows no smooth variation of τ with M_2. Since many of the solutes are solid at room temperature, the relation between τ and molar volume, taken as M_2/d_2, cannot be completely considered, although signs of a rough dependence may be seen for those compounds which are liquid. Various empirical and other properties of the substances listed have been plotted against τ; *e.g.*, the curve of parachor (P) versus τ included all the values of τ within a rather wide "corridor." This was of interest since parachors provide relative measures of molecular volumes and can be computed with fair accuracy from known atom and bond "constants" (the figures in parentheses in Table 4 were estimated in this way from Vogel's Table XXII of *J.*, 1948, 1833; the remainder are measurements given in Vogel's various papers). Neither the plot of the product ABC (see later) nor that of the quotient $\mu^2/3kT$ against τ was at all satisfactory; they were tried because they had the same order of magnitude (*viz.*, 10^{-24} c.c.) as has r^3 in equation (1). A graph of R_2 against τ was suggestive: it contained all points in a band no

Table 4. *Molecular dimensions, parachors, and refractivities.*

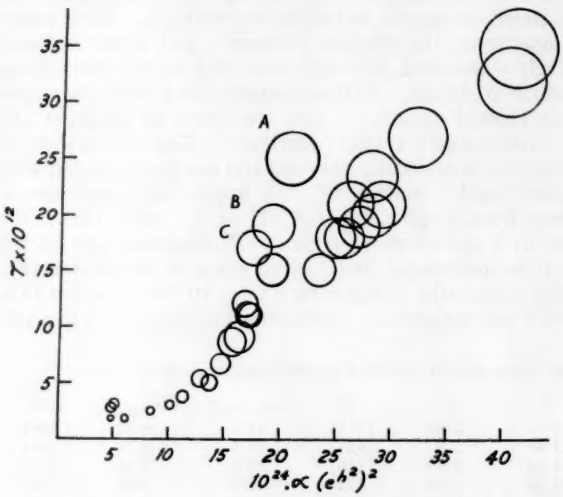
	A	B	C	P	R_D (c.c.)	$10^{24}\alpha_{mean}$	$10^8\bar{h}^2$
CH_3Cl	5·27	3·80	3·80	(111)	11·5	4·53	26·1
CH_3Br	5·54	3·80	3·80	(124)	14·5	5·71	35·1
CH_3I	5·92	3·80	3·80	(146)	19·4	7·64	49·2
$CH_3{\cdot}NO_2$	5·20	4·50	3·80	132	12·5	4·93	16·1
$CH_3{\cdot}CN$	5·95	3·80	3·80	122	11·1	4·37	50·4
$C_6H_5{\cdot}CH_3$	8·25	6·05	3·80	247	31·1	$12·2_5$	90·7
C_6H_5F	7·33	6·05	2·90	214	26·0	10·2	118
C_6H_5Cl	8·08	6·05	3·16	244·5	31·1	$12·2_5$	123
C_6H_5Br	8·20	6·05	3·40	261	33·9	13·4	111
C_6H_5I	8·58	6·05	3·64	282	39·1	15·4	110
$C_6H_5{\cdot}CN$	8·95	6·05	2·90	259	31·4	12·4	171·5
$C_6H_5{\cdot}NO_2$	8·00	6·05	2·90	264·5	32·7	12·9	138
o-Xylene	7·50	6·80	3·80	283	35·8	14·1	$70·7_5$
m-Xylene	6·80	8·70	3·80	284	35·9	14·1	98·3
$4\text{-}C_6H_5{\cdot}C_6H_4{\cdot}Cl$	12·40	6·05	3·16	(419)	57·8	22·8	287
$4\text{-}C_6H_5{\cdot}C_6H_4{\cdot}NO_2$	12·32	6·05	2·90	(435)	56·4	22·2	305
$1\text{-}C_{10}H_7{\cdot}NO_2$	8·00	8·70	2·90	(369)	$50·0_5$	19·7	156·5
$p\text{-}Cl{\cdot}C_6H_4{\cdot}NO_2$	9·41	6·05	3·16	(303)	37·5	14·8	169
$p\text{-}CH_3{\cdot}C_6H_4{\cdot}NO_2$	9·57	6·05	3·80	303	37·4	14·7	135
CMe_3Cl	6·80	6·88	6·88	(225)	25·8	10·2	0·0
CMe_3Br	7·05	6·88	6·88	(239)	28·9	11·4	0·1
CMe_3I	7·46	6·88	6·88	(260)	34·6	13·6	1·5
$\alpha\text{-}C_{10}H_7F$	7·34	8·70	2·90	321	43·7	17·2	154
β- ,,	9·79	7·30	2·90	(321)	43·7	17·2	183
$\alpha\text{-}C_{10}H_7Cl$	8·00	8·70	3·16	(350)	49·2	19·4	138
β- ,,	10·44	7·30	3·16	(350)	49·4	19·5	183
$\alpha\text{-}C_{10}H_7Br$	8·28	8·70	3·40	(363)	51·6	20·3	125
β- ,,	10·71	7·30	3·40	(363)	51·8	20·4	175
$\alpha\text{-}C_{10}H_7I$	8·60	8·70	3·64	(386)	56·5	22·3	114·5
β- ,,	11·02	7·30	3·64	(386)	57·9	22·8	169

wider than that of the parachor–τ plot, and placed related molecules (*e.g.*, fluoro-, chloro-, bromo-, and iodo-benzenes) on individual straight lines having different inclinations to the τ-axis.

When either parachors or refractivities were used, however, the three *tert.*-butyl halides stood on the lower fringe of the "corridor," as though their τ's were abnormally low. Now, the small relaxation times of certain molecules of a near-spherical form have been noted by several workers (*e.g.*, Smyth, *Trans. Faraday Soc.*, 1946, **42**, *A*, 175; Böttcher, *op. cit.*, Chap. 10); it seemed, therefore, that multiplication of the parachors or refractivities by "shape factors" would improve the curves in question.

The dimensions given in Table 4 have been used as a basis. Their derivations from scale-drawings, etc., are explained in the papers by Le Fèvre and his colleagues cited on

p. 2873. Of various ratios and combinations of A, B, and C, that denoted as h^2 by Holland and Le Fèvre (*J.*, 1950, 2166) seemed to be most suitable (numerical values of h^2 are quoted in Table 4).



Empirical correlation of the relaxation times (τ) with shape factors and mean polarisabilities (see below), incorporating estimated experimental errors.

The figure depicts the best relationship, *viz.*, $10^{12}\tau$ plotted against the product 10^{24} (α_{mean}) (exp $h^2)^2$, so far extracted from the present data. (The average polarisability (α_{mean}) is directly calculable from the molecular refraction R.) The closeness of the points makes provision of a key difficult; A, B, and C, which are most out-of-line, refer respectively to *p*-chloronitrobenzene in carbon tetrachloride, *p*-nitrotoluene in benzene, and benzonitrile in carbon tetrachloride. In addition to experimental errors, and to the use of non-uniform temperatures, its imperfections must be, in part, due to neglect of solvent effects. The work of, *inter al.*, Whiffen (*Trans. Faraday Soc.*, 1950, **46**, 130) indicates that a given medium will not influence the τ's of all molecules alike (*e.g.*, the relaxation times of nitrobenzene and camphor are slightly greater in carbon tetrachloride than in benzene; for chloroform the reverse is true). Hill (*Nature*, 1953, **171**, 836) has plotted τ against the " mutual viscosities " for solute–solvent pairs made by six solutes and three solvents; an approximation to a straight line through the origin resulted. However, the Figure embraces a wider range of relaxation times and a greater number of solutes than were considered by Hill; further, it appears to do so more smoothly.

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The Solubility of Ethyl Acetate in Some Perchlorate and Nitrate Solutions.

By (Mrs.) G. M. Waind.

[Reprint Order No. 5342.]

The solubility of ethyl acetate at 25° has been measured in 0·25—1M-aqueous solutions of lithium, silver, and sodium perchlorate and nitrate, and also of potassium nitrate. The perchlorates salt in and the nitrates salt out: the effect of the different cations is much smaller. In mixtures of these perchlorates and nitrates at constant ionic strength the salting-in effect of the perchlorate ion can be described by the association constant (K = 0·52 ± 0·02) of a 1 : 1-ethyl acetate–perchlorate complex.

Although numerous studies of the solubility of ethyl acetate in aqueous electrolyte solutions have been made (for summary see Altshuller and Everson, *J. Amer. Chem. Soc.*, 1953, **75**, 4823) and the anomalously small salting-out effect of the iodide ion noted, salting in has only been reported for large cations. It was decided to measure the solubility of ethyl acetate in some perchlorate solutions and to compare this with its solubility in the corresponding nitrates.

Experimental and Results

Materials.—Ethyl acetate was washed with aqueous potassium carbonate solution and water, dried over anhydrous potassium carbonate, and redistilled. All the salts were either "AnalaR" grade or were recrystallised and dried. The silver solutions were standardised gravimetrically as chloride, and the lithium solutions as sulphate.

Method.—A measured volume of each salt solution was shaken with a slight excess of ethyl acetate and the mixture left in a thermostat at either 25° ± 0·01° or 35° ± 0·01° for 2 hr.; 5 c.c. of the aqueous phase were then removed and the dissolved ethyl acetate determined by titration. With the silver solutions the ester was distilled into excess of sodium hydroxide solution. The densities were determined with a density bottle.

Results.—The results are given in Tables 1 and 2, where M_S = molarity of salt; M_E = molarity of ethyl acetate; S = g. of ethyl acetate per 100 g. of solvent; m = molality; $\gamma = S_0/S$; and S_0 = the solubility of ethyl acetate in water. The densities are those of the salt solutions saturated with ethyl acetate.

Table 1.

Temp., 25°.

Salt	M_S	M_E	Density	S	γ	M_S	M_E	Density	S	γ
—	—	0·8426	0·9957	8·048	—	—	—	—	—	—
$NaClO_4$	1	0·9376	1·066	9·583	0·8399	0·5	0·8867	1·031	8·750	0·9198
	0·75	0·9128	1·048	9·173	0·8772	0·25	0·8632	1·013	8·383	0·9601
$NaNO_3$	1	0·7058	1·048	6·900	1·166	0·5	0·7740	1·022	7·474	1·076
	0·75	0·7395	1·035	7·201	1·118	0·25	0·8010	1·009	7·685	1·047
KNO_3	1	0·7078	1·053	7·001	1·149	0·5	0·7761	1·024	7·548	1·066
	0·75	0·7406	1·039	7·257	1·109	0·25	0·8056	1·010	7·757	1·038
$AgNO_3$	1	0·7612	1·126	7·536	1·068	0·5	0·7868	1·061	7·635	1·054
	0·75	0·7709	1·094	7·550	1·066	0·25	0·8123	1·028	7·823	1·029
$AgClO_4$	1	1·008	1·141	10·49	0·7672	0·5	0·9026	1·069	8·960	0·8917
	0·75	0·9605	1·105	9·777	0·8231	0·25	0·8700	1·033	8·465	0·9510
$LiNO_3$	1	0·7722	1·033	7·600	1·059	0·5	0·7905	1·014	7·640	1·053
	0·75	0·7770	1·024	7·575	1·063	0·25	0·8130	1·005	7·810	1·030
$LiClO_4$	1	1·094	1·050	11·35	0·7091	0·5	0·9330	1·022	9·242	0·8708
	0·75	1·008	1·036	10·22	0·7875	0·25	0·8775	1·009	8·535	0·9430
Temp., 35°.										
—	—	0·7591	0·9926	7·216						
$NaNO_3$	1	0·6246	1·043	6·088	1·185					
$NaClO_4$	1	0·8468	1·061	8·624	0·8368					

TABLE 2.

M_{XNO_3}	M_{XClO_4}	M_E	Density	m_{XClO_4}	m_E	K
			Temp., 25°.			
$NaNO_3$–$NaClO_4$						($k_1 = 0.758$)
0·75	0·25	0·745	1·052	0·286	0·836	0·50
0·5	0·5	0·806	1·057	0·560	0·914	0·51
0·25	0·75	0·867	1·062	0·859	0·994	0·50
0	1	0·938	1·066	1·116	1·088	0·52
$AgNO_3$–$AgClO_4$						($k_1 = 0.819$)
0·75	0·25	0·795	1·129	0·284	0·904	0·52
0·5	0·5	0·850	1·133	0·575	0·979	0·52
0·25	0·75	0·919	1·137	0·852	1·072	0·52
0	1	1·008	1·141	1·184	1·194	0·57
$LiNO_3$–$LiClO_4$						($k_1 = 0.844$)
0·75	0·25	0·825	1·038	0·282	0·931	0·53
0·5	0·5	0·903	1·042	0·566	1·020	0·53
0·25	0·75	0·960	1·047	0·866	1·110	0·53
0	1	1·094	1·050	1·180	1·291	0·72
			Temp., 35°.			
$NaNO_3$–$NaClO_4$						($k_1 = 0.658$)
0·75	0·25	0·661	1·048	0·280	0·738	0·61
0·5	0·5	0·717	1·053	0·565	0·810	0·56
0·25	0·75	0·783	1·057	0·857	0·894	0·58
0	1	0·847	1·061	1·156	1·001	0·64

DISCUSSION

The chief feature of the results is that the perchlorates increase the solubility of ethyl acetate in water, while the nitrates, like all other anions that have been studied, salt out. The order of the salting out of the cations is Na > K > Ag > Li. Potassium and sodium nitrate and sodium perchlorate obey the Setchenow equation, $\log_{10} \gamma = kM_{salt}$; k for potassium nitrate agrees with that calculated from Glasstone's results (Glasstone, Dimond, and Jones, *J.*, 1926, 2935), that for sodium nitrate is slightly lower. The effects of the silver and lithium salts are not linear but are approximately so up to an ionic strength of about 0·5. The value of the solubility of ethyl acetate in water at 25° is the same as that given by Altshuller and Everson (*J. Amer. Chem. Soc.*, 1953, **75**, 1727), that at 35° is 2% lower.

The salting in of ethyl acetate by perchlorate ions appears to be directly comparable with the increased solubility of ethyl methyl ketone in perchlorate solutions, described by Duclaux and Durand-Gasselin (*J. Chim. phys.*, 1938, 189), and of γ-butyrolactone in sodium perchlorate solutions (Long, McDevit, and Dunkle, *J. Phys. Colloid Chem.*, 1951, **55**, 814). Table 3, in which values of the Setchenow constant as defined above, at 25°, for γ-butyrolactone are compared with those calculated from recent data for ethyl acetate, shows that this similarity also applies to solutions of alkali halides.

TABLE 3.

Salt	NaCl	NaBr	NaI	$NaClO_4$
γ-Butyrolactone	0·067	0·007	−0·088	−0·113
Ethyl acetate	0·189	0·119	0·026	−0·076

It is well known that in order to account for the salting in of non-electrolytes it is necessary to consider short-range forces between the ions, solvent, and non-electrolyte, in addition to the electrostatic effect of the ions (Debye effect) and the volume occupied by the non-electrolyte (McDevit and Long, *J. Amer. Chem. Soc.*, 1952, **74**, 1775: *Chem. Reviews*, 1952, **51**, 119). The reasons for these short-range forces have been much discussed (*e.g.* Bockris, Kitchener, and Bowler-Reed, *Trans. Faraday Soc.*, 1951, **47**, 184; Saylor, Whitten, Claiborne, and Gross, *J. Amer. Chem. Soc.*, 1952, **74**, 1778). The data collected in Table 2 for nitrate–perchlorate mixtures at constant ionic strength of 1 can be used to show that in these solutions this effect can be adequately described by means of the association constant of an ethyl acetate–ClO_4^- complex.

The solubility of the ester in the mixed salt solutions can be expressed as $m_E = k_1 + k_2 . m_{XClO_4}$, where k_1 and k_2 are constants for each cation at 25° [k_2 has the same value (0·276) for the sodium solutions at 25° and 35°]. If it is assumed that the molality of the uncomplexed ethyl acetate is the same at constant temperature in all the solutions containing perchlorate ions and with the same cation at constant ionic strength this equation may be rewritten as $m_E = m_E$ (free) + $m_{complex}$.

Values of an association constant K, defined by $K = m_{complex}/k_1 (m_{XClO_4} - m_{complex})$ are included in Table 2.

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The Reaction between NN-*Di-2′-chloroalkyl-2-naphthylamines and 4-Amino-5-nitrosopyrimidines.*

By D. G. I. FELTON and G. M. TIMMIS.

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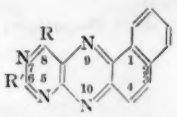
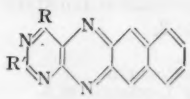
The reaction between 2 : 4 : 6-triamino-5-nitrosopyrimidine and *NN*-di-2′-chloroethyl- or *NN*-di-2′-chloropropyl-2-naphthylamine in acetic acid in the presence of anhydrous sodium acetate yields 6 : 8-diamino-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = R′ = NH_2), which is also, and better, obtained by fusion of 2 : 4 : 6-triamino-5-nitrosopyrimidine with 2-naphthol at 150°. 4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine and *NN*-di-2′-chloroethyl-2-naphthylamine yield (I; R = NH_2, R′ = MeS). In efforts to elucidate the course of this reaction, it has been shown that trimethyl-2-naphthylammonium iodide, in the presence of both 4-amino-5-nitrosopyrimidines mentioned and anhydrous sodium acetate, yields 3 : 4-6 : 7-dibenzacridine methiodide (IV), whereas triethyl-2-naphthylammonium iodide yields triethyl-2-naphthylammonium periodide with triaminonitrosopyrimidine.

IN some exploratory attempts to synthesise heterocyclic systems which have analogies with the pteridine series and might possess antifolic acid or antifolinic acid (anticitrovorum factor, antileucovorin) activity, it was observed that 2 : 4 : 6-triamino-5-nitrosopyrimidine reacted with the biologically active aromatic nitrogen " mustard," *NN*-di-2′-chloroethyl-2-naphthylamine (Ross, *J.*, 1949, 183), in glacial acetic acid solution in the presence of anhydrous sodium acetate to yield a sparingly soluble, yellow, high-melting solid (A), exhibiting a very intense yellowish-green fluorescence in solution in glacial acetic acid. Analysis characterised it as $C_{14}H_{10}N_6$ although, at first, the existence of hydrates tenaciously holding water complicated the results. 4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine and the same aromatic amine gave a very small yield of an analogous compound, $C_{15}H_{11}N_5S$. This type of reaction did not take place when a number of substituted *NN*-di-2′-chloroethylanilines were employed; but *NN*-di-2′-chloropropyl-2-naphthylamine (Everett and Ross, *J.*, 1949, 1972) and 2 : 4 : 6-triamino-5-nitrosopyrimidine gave the same yellow product (A). This surprising result implied that the di-2-chloroalkyl group was not involved in the final product, while the formulæ of the products and the dependence on the nature of the aryl substituent of the aromatic amine suggested that the naphthalene moiety was somehow united with the pyrimidine molecule. Consequently the di-2-chloroalkylamino-group must be ejected during the reaction.

From these considerations the structures (I; R = R′ = NH_2) and (I; R = NH_2, R′ = MeS) were proposed for the products (A; $C_{14}H_{10}N_6$) and $C_{15}H_{11}N_5S$; structure (II) is much less likely since the 2-dialkylamino-group will probably activate position 1 of the naphthalene molecule and the colour of (A) is much lighter than that of the linear benzalloxazine (Ross, *J.*, 1948, 219).

Compounds of structure (I) have been recorded (Kühling, *Ber.*, 1891, **24**, 2363, 3031; Kuhn and Cook, *Ber.*, 1937, **70**, 761; Ross, *loc. cit.*) but all were obtained by condensation of a 1 : 2-diaminonaphthalene with alloxan or of a 1 : 2-naphthaquinone with a 4 : 5-diaminopyrimidine, neither of these routes yielding an unambiguously orientated product. Where one of the azine nitrogen atoms (9 or 10) is substituted, *e.g.*, by a sugar residue or

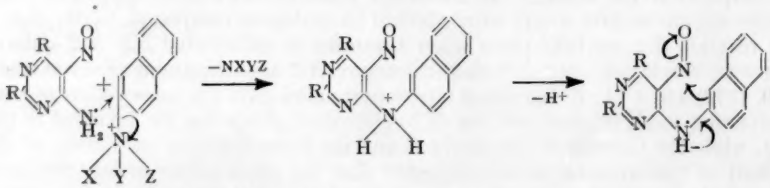
(I)   (II)

alkyl group (Karrer and Quibell, *Helv. Chim. Acta*, 1936, **19**, 1034; Lettré and Fernholz, *Ber.*, 1940, **73**, 436; Ross, *loc cit.*) then, of course, an unambiguously orientated benz*iso*-alloxazine is formed. It appeared probable that the product (A) consisted of one isomer only, *viz.*, that shown.

In an effort to obtain compounds of structure (I) in high yield a study was made of the conditions of the reaction. Alkaline catalysis by sodium 2-ethoxyethoxide in 2-ethoxyethanol, or by anhydrous potassium carbonate in the same solvent failed to bring about the reaction at all, as did heating the components in glacial acetic acid alone. The maximum yield was obtained when two mols. of aromatic amine were used together with two of sodium acetate for one of the triaminonitrosopyrimidine.

In view of the poor yields which this reaction afforded, an examination was made of the methods of synthesis available for the related 1 : 2-benzophenazine series. That due to Ullmann and Ankersmit (*Ber.*, 1905, **38**, 1811), in which a 2 : 4-diaminoazobenzene derivative (chrysoidine) was fused with 2-naphthol, seemed promising; and by regarding 2-naphthol as the enol of a cyclic ketone, a still closer analogy may be found in the unambiguous synthesis of 6 : 7-unsymmetrically substituted pteridines by the reaction of 4-amino-5-nitrosopyrimidines with α-keto-methylene compounds described by one of us (*Nature*, 1949, **164**, 139; and unpublished work). Accordingly, 2 : 4 : 6-triamino-5-nitrosopyrimidine was fused at 150° with 2-naphthol: the product (I; R = R′ = NH_2) was isolated from the melt in nearly quantitative yield.

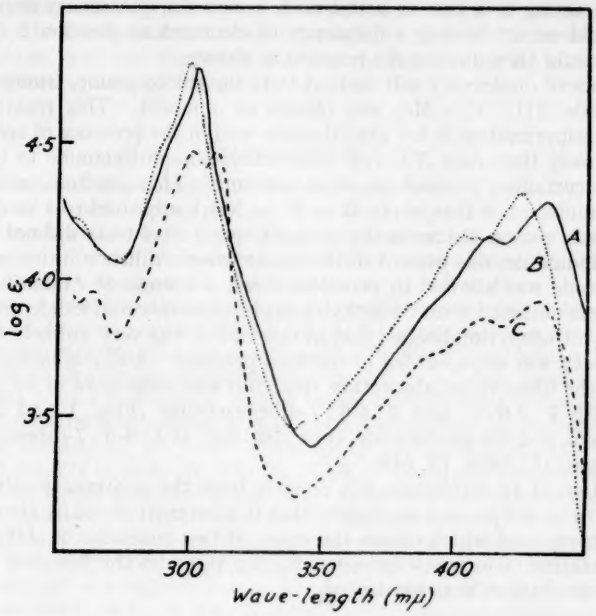
In considering the course of the reaction it was thought initially that its extremely weak basicity was responsible for the ejection of the di-2-chloroalkylamino-group from the naphthalene molecule; but using the corresponding weakly basic alcohol, *NN*-di-2′-hydroxyethyl-2-naphthylamine, we were unable to isolate any trace of compound (I; R = R′ = NH_2). Attempts to cause non-basic or weakly basic derivatives of 2-naphthylamine, *viz.*, *NN*-di-2′-acetoxyethyl-2-naphthylamine, 2-acetamidonaphthalene, or *N*-benzylidene-2-naphthylamine, to react with 2 : 4 : 6-triamino-5-nitrosopyrimidine failed, as did that with 2-naphthylamine hydrochloride. Thus no reaction occurred in the absence of halogen. This suggested that either inter- or intra-molecular quaternisation of the chloro-amine was necessary, the former being the more likely as the maximum yield of (I; R = R′ = NH_2,



or R = NH_2, R′ = MeS) occurred when two molecular proportions of the amine were taken.

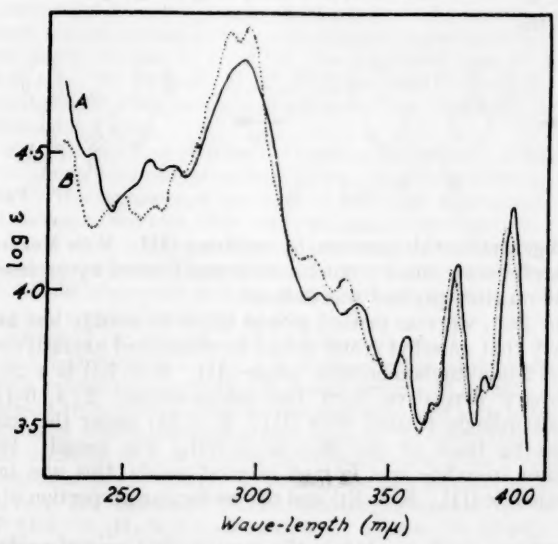
All attempts to isolate a quaternary salt of the aromatic nitrogen mustards have so far failed (Everett and Ross, *loc. cit.*) and we were unable to form the methiodide of *NN*-di-2′-hydroxyethyl-2-naphthylamine. Assuming, however, that quaternisation did occur to a slight extent in solution—and Ross and his co-workers do not exclude entirely the transitory

FIG. 1. *Ultra-violet absorption spectra.*



A, 3 : 4-6 : 7-*Dibenzacridine methoidide.*
B, 3 : 4-6 : 7-*Dibenzacridine.*
C, 1 : 2-6 : 7-*Dibenzacridine.*
(*Solvent:* 4·5% *formic acid for A;* 36% *formic acid for B and C*).

FIG. 2. *Ultra-violet absorption spectra.*

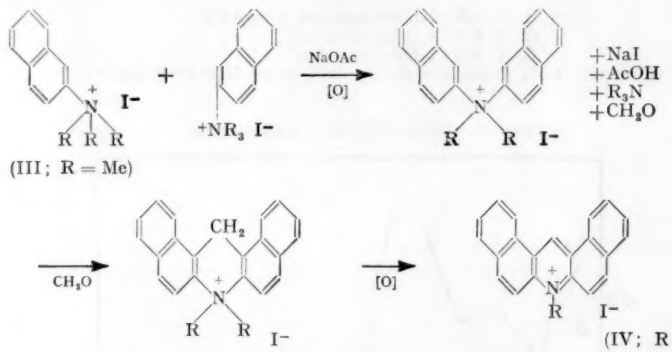


A, 3 : 4-6 : 7-*Dibenzacridine.*
B, 1 : 2-6 : 7-*Dibenzacridine.*
(*Solvent:* 95% *ethanol*).

existence of such compounds in solution—it is conceivable that under the influence of the sodium acetate, acting as a base in acetic acid, loss of the quaternary group as a tertiary alkylamine would occur, leaving a deficiency of electrons at position 2 of the naphthyl residue, which could then initiate the reaction as shown.

In the absence of quaternary salt derived from the chloro-amine, trimethyl-2-naphthylammonium iodide (III; R = Me) was chosen as a model. This reacts with 2 : 4 : 6-triamino-5-nitrosopyrimidine in hot glacial acetic acid in the presence of anhydrous sodium acetate more slowly than does *NN*-di-2'-chloroethyl-2-naphthylamine to yield an orange-yellow highly crystalline product in small amount. This product, which possessed a fluorescence reminiscent of that of (I; R = R' = NH_2), appeared to a be quaternary salt: although for some reason unknown the ordinary qualitative tests did not reveal the presence of iodine, iodide ion was present in the eluate when a dilute solution of the compound in aqueous acetone was allowed to percolate down a column of Amberlite IR-120. The same product was obtained from trimethyl-2-naphthylammonium iodide and 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine, so that in this case it was very unlikely that the nitrosopyrimidine moiety was incorporated in the final product. Analysis indicated the formula $C_{22}H_{16}NI$ and the ultra-violet absorption spectrum was suggestive of an acridine system. Comparison with 1 : 2-6 : 7- and 3 : 4-6 : 7-dibenzacridine (Figs. 1 and 2) indicated the latter ring system, and the product was then identified as 3 : 4-6 : 7-dibenzacridine methiodide (IV) (Morgan, *J.*, 1898, **73**, 548).

This formation of an acridinium salt directly from the quaternary salt of an aromatic amine appears to be unique and we suggest that it is brought about by the oxidative action of the nitroso-compound which causes the union of two molecules of (III; R = Me) with concurrent formation of formaldehyde, which then provides the bridging carbon atom 5. The suggested mechanism is as illustrated.



An attempt to generalise this reaction, by oxidising (III; R = Me) to (IV) by means of chromic acid in acetic acid, failed: much iodine was formed by preferential oxidation of the iodide ion, and no other product was isolated.

It was thought that, whereas methyl groups might be readily lost as formaldehyde, it would be less likely that an ethyl group would be eliminated oxidatively as acetaldehyde. Moreover, triethyl-2-naphthylammonium iodide (III; R = Et) is a closer model for the suggested quaternary derivative from the chloro-amine. 2 : 4 : 6-Triamino-5-nitrosopyrimidine was accordingly treated with (III; R = Et) under the conditions obtaining earlier, but again no trace of (I; R = R' = NH_2) was found. Instead, triethyl-2-naphthylammonium tri-iodide was formed in good yield; this was independently synthesised from the iodide (III; R = Et) and one molecular proportion of iodine in aqueous ethanol.

A final attempt was made to obviate the complicating ease of oxidation of the iodide anion by treating 2 : 4 : 6-triamino-5-nitrosopyrimidine with triethyl-2-naphthylammonium chloride, a still closer analogy to the quaternary salt which we conjecture to be formed

from the chloro-amine but lacking 2′-chloro-substituents. However, prolonged heating did not cause any reaction.

In conclusion, the condensation of the chloro-amine to give the tetra-azabenzanthracene remains unique, and our suggested reaction mechanism for it, although plausible, remains tentative and unsubstantiated.

Experimental

M p.s were determined in an electrically heated copper block. Some of the analyses were done by Mr. F. Oliver, Imperial College of Science and Technology, S.W.7. Fluorescence observations were made in ultra-violet light from a Hanovia lamp, and ultra-violet absorption spectra were determined with a Unicam photoelectric spectrophotometer, Model SP. 500.

6 : 8-*Diamino*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = R′ = NH_2).—(a) *Reaction of* NN-*di*-2′-*chloroethyl*-2-*naphthylamine with* 2 : 4 : 6-*triamino*-5-*nitrosopyrimidine.* A mixture of *NN*-di-2′-chloroethyl-2-naphthylamine (16·2 g.), 2 : 4 : 6-triamino-5-nitrosopyrimidine (4·5 g.), and anhydrous sodium acetate (5·1 g.) in glacial acetic acid (60 ml.) was refluxed for 2 hr. during which the insoluble nitroso-compound was slowly replaced by a yellow precipitate. This was collected, extracted with hot water to remove traces of unchanged nitroso-compound, and crystallised several times from 80% formic acid, in which it appeared to be converted into a *formate*, pale yellow felted needles, m. p. >400° (Found: C, 57·4, 57·3; H, 4·2, 3·9; N, 27·4. $C_{14}H_{10}N_6,H{\cdot}CO_2H$ requires C, 58·5; H, 3·9; N, 27·3%). Consequently a hot solution in 80% formic acid was filtered into an excess of hot dilute aqueous ammonia, and the golden-yellow precipitate of 6 : 8-*diamino*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = R′ = NH_2), m. p. >400°, was washed with hot water, ethanol, and ether in succession and dried at 100°/0·1 mm. (Found: C, 62·8; H, 3·9; N, 31·8. $C_{14}H_{10}N_6,\frac{1}{4}H_2O$ requires C, 63·0; H, 3·9; N, 31·5. Found, on a sample dried at 150° in a high vacuum immediately before analysis: C, 63·6; H, 4·1; N, 31·9. $C_{14}H_{10}N_6$ requires C, 64·1; H, 3·8; N, 32·05%). Ultra-violet absorption max. in 4·5% formic acid solution: 281 (log ε 4·26), 291 (log ε 4·28), 302 (log ε 4·32), and 413 mμ (log ε 4·18). In dilute solution in glacial acetic acid the compound exhibited an intense yellow-green fluorescence. It gave a cherry-red colour in concentrated sulphuric acid. The *diacetamido*-derivative formed primrose-yellow needles, m. p. 322° (decomp.), from glacial acetic acid (Found: C, 61·8; H, 4·2; N, 23·6. $C_{18}H_{14}O_2N_6,\frac{1}{4}H_2O$ requires C, 61·6; H, 4·1; N, 24·0%).

(b) *Reaction of* NN-*di*-2′-*chloropropyl*-2-*naphthylamine with* 2 : 4 : 6-*triamino*-5-*nitrosopyrimidine.* *NN*-Di-2′-chloropropyl-2-naphthylamine (2·96 g.), 2 : 4 : 6-triamino-5-nitrosopyrimidine (0·8 g.), and anhydrous sodium acetate (0·8 g.) were refluxed in glacial acetic acid (10 ml.) for 2 hr. The yellow precipitate, worked up as in (a), was a *hydrated* base, m. p. >400° (Found: C, 60·6, 60·8; H, 4·2, 4·15; N, 30·7. $C_{14}H_{10}N_6,\frac{3}{4}H_2O$ requires C, 61·0; H, 4·2; N, 30·5%). Ultra-violet absorption max. in 4·5% formic acid solution: 281 (log ε 4·26), 291 (log ε 4·27), 302 (log ε 4·32), and 413 mμ (log ε 4·18).

(c) *Reaction of* 2-*naphthol with* 2 : 4 : 6-*triamino*-5-*nitrosopyrimidine.* 2-Naphthol (4·5 g.) was melted and 2 : 4 : 6-triamino-5-nitrosopyrimidine (1·54 g.) was stirred into it when the internal temperature was 130°. The temperature was held at 150° with intermittent stirring for 2 hr. The melt was cooled and extracted with ether, and the insoluble residue (2·56 g.) was thoroughly washed with ethanol and ether. Recrystallisation from 80% formic acid followed by a treatment with dilute ammonia afforded the tetra-aza-1 : 2-benzanthracene (I; R = R′ = NH_2), identified by the ultra-violet absorption in 4·5% formic acid solution: $\lambda_{max.}$ 281 (log ε 4·25), 291 (log ε 4·28), 302 (log ε 4·31), and 413 mμ (log ε 4·16).

8-*Amino*-6-*methylthio*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = NH_2, R′ = MeS).—*NN*-Di-2′-chloroethyl-2-naphthylamine (2·7 g.), 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine (0·9 g.), and anhydrous sodium acetate (0·9 g.) in glacial acetic acid (20 ml.) were refluxed for 2 hr. and the solid obtained after cooling and collection was triturated with water, yielding a green solid (0·7 g.). Unchanged nitroso-compound was removed by extraction with boiling water (7 × 50 ml.), and the insoluble residue purified by crystallisation from 2-ethoxyethanol. The *tetra-aza*-1 : 2-*benzanthracene* (I; R = NH_2, R′ = MeS) formed greenish-yellow leaflets with a strong golden lustre, m. p. 330° (decomp.) (Found, in a sample dried at 140° in a high vacuum: C, 61·9; H, 4·2; N, 24·1. $C_{15}H_{11}N_5S$ requires C, 61·5; H, 3·8; N, 23·9%). The compound gives a cherry-red colour with concentrated sulphuric acid and exhibits an intense yellow-green fluorescence in glacial acetic acid.

3 : 4-6 : 7-*Dibenzacridine Methiodide* (IV).—(a) *Reaction of trimethyl*-2-*naphthylammonium*

iodide with 2 : 4 : 6-*triamino-5-nitrosopyrimidine.* 2 : 4 : 6-Triamino-5-nitrosopyrimidine (1·54 g.), trimethyl-2-naphthylammonium iodide (6·26 g.), and anhydrous sodium acetate (1·64 g.) were refluxed in glacial acetic acid (30 ml.). After 1 hr. precipitation of orange crystals began and the mixture was filtered hot after 5 hr. The orange solid (2·18 g.) so obtained was dissolved in hot aqueous-ethanolic sodium hydroxide, and the solution filtered and acidified with acetic acid, yielding a precipitate (1·29 g.). This was then further purified by crystallisation from 80% formic acid and finally from 50% formic acid, to yield lustrous orange-yellow prisms, m. p. 284° (decomp.), undepressed on admixture with 3 : 4-6 : 7-dibenzacridine methiodide [Morgan, *loc. cit.*, gives m. p. 262—264° (decomp.)] (Found : C, 62·5, 63·0; H, 3·8, 3·95; N, 3·3, 3·6; I, 29·6; NMe, 6·9. Calc. for $C_{22}H_{16}NI$: C, 62·7; H, 3·8; N, 3·3; I, 30·1; NMe, 6·9%. A Rast determination could not be carried out owing to the insolubility of the compound in camphor). Ultra-violet absorption spectrum max. in 4·5% formic acid : 302 (log ε 4·78), 412 (log ε 4·16), and 434 mμ (log ε 4·29).

(b) *Reaction of trimethyl-2-naphthylammonium iodide with* 4 : 6-*diamino-2-methylthio-5-nitroso-pyrimidine.* Trimethyl-2-naphthylammonium iodide (3·13 g.) in glacial acetic acid (20 ml.) with 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine (0·92 g.) and anhydrous sodium acetate (0·82 g.), treated as in (a), gave the same orange-yellow prisms (0·55 g., crude) m. p. and mixed m. p. 284° (decomp.) (Found : C, 62·3; H, 3·7%), having the recorded ultra-violet absorption max. in 4·5% formic acid. Addition of ether to the mother-liquors from the reaction gave a buff precipitate, which was boiled with aqueous-ethanolic sodium hydroxide; the resulting pale orange solution was filtered and acidified with acetic acid. No precipitate was obtained but the addition of saturated ethanolic picric acid afforded a *picrate*, yellow needles (from ethanol), m. p. 195°, undepressed on admixture with authentic trimethyl-2-naphthylammonium picrate (Ingham, *J.*, 1927, 1972) (Found : C, 55·4; H, 4·4. $C_{19}H_{18}O_7N_4$ requires C, 55·1; H, 4·4%).

Triethyl-2-naphthylammonium Periodide.—(*a*) Triethyl-2-naphthylammonium iodide (0·5 g.) was dissolved in a mixture of water (20 ml.) and ethanol (5 ml.). Iodine solution (29·25 ml. of 0·965 × 0·1N-iodine) was added and the dark red precipitate (yield quantitative) was collected after thorough chilling. When crystallised from ethanol, the *tri-iodide* formed dark red needles with a steely-blue lustre, m. p. 99° (Found : C, 31·9; H, 3·9; N, 2·3; I, 63·2. $C_{46}H_{22}NI_3$ requires C, 31·7; H, 3·6; N, 2·3; I, 62·5%). The tri-iodide, in hot water, yields the characteristic blue colour with starch solution.

(*b*) Triethyl-2-naphthylammonium iodide (3·55 g.) was heated with a suspension of 2 : 4 : 6-triamino-5-nitrosopyrimidine (0·78 g.) and anhydrous sodium acetate (0·82 g.) in glacial acetic acid (20 ml.). The precipitate of greenish-brown iridescent needles (1·5 g.) was collected after 4 hr. and crystallised from 80% formic acid, yielding the tri-iodide as dark red needles with a blue sheen, m. p. and mixed m. p. 98—99°. The mother-liquors afforded only dark oils.

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The Synthesis of Compounds with Potential Anti-folic Acid Activity. Part I. 7-Amino- and 7-Hydroxy-pteridines.

By R. G. W. Spickett and G. M. Timmis.

[Reprint Order No. 5082.]

The unequivocal synthesis is reported of a number of 7-amino- and 7-hydroxy-pteridines by the reaction of 4-amino-5-nitrosopyrimidines with phenylacetonitriles and phenylacetyl chlorides respectively. Sodium alkoxides were effective catalysts for the reaction with the acetonitriles. Reaction of 2 : 4 : 6-triamino-5-nitrosopyrimidine with arylacetyl chlorides was best in the absence of a solvent. 2 : 4-Diamino-7-hydroxy-6-phenylpteridine thus obtained was also formed by treating phenylglyoxylic acid with 2 : 4 : 5 : 6-tetra-aminopyrimidine hydrochloride at pH 5: in more acid solution the isomeric 7-phenylpteridine was a minor product.

Hydroxy-groups are introduced into the 2-position by hydrolysis of 2-methylthiopteridines and into the 4-position by hydrolysis of 2 : 4 : 7-triamino-6-phenylpteridine.

Some of the 7-amino-6-arylpteridines show anti-folic acid activity but in no case of a high order.

The first simple derivatives of pteridine to show marked anti-folic acid activity were synthesised by Mallette, Taylor, and Cain (*J. Amer. Chem. Soc.*, 1947, **69**, 1814), and Daniel *et al.* (*J. Biol. Chem.*, 1947, **169**, 689; **170**, 747) found that, in general, the replacement of hydroxy-groups in the 2- and the 4-position by the amino-group successively led to greatly enhanced activity. Maximum activity in antagonising the folic acid required for growth by certain micro-organisms was shown by 2 : 4-diamino-6 : 7-diarylpteridines and in the hope of further enhancing activity we wished to replace one of the aryl groups by an amino- and also by a hydroxy-group.

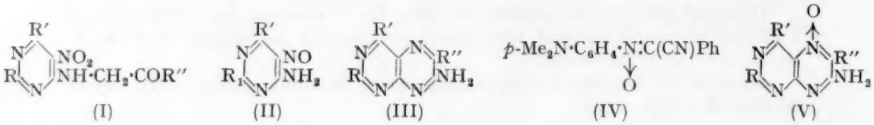
Hitherto (for summaries, see *Ann. Reports*, 1946, **43**, 250; 1948, **45**, 226; Gates, *Chem. Reviews*, 1947, **41**, 63; Albert, *Quart. Reviews*, 1952, **6**, 197) three general methods have been used for the synthesis of pteridines. Condensation of 4 : 5-diaminopyrimidines with α-diketones and related substances is the most frequently used method, but suffers from the major drawback that from an unsymmetrical dicarbonyl compound two isomers can be formed of necessarily undetermined constitution and in some cases difficultly separable. Ring closure of certain substituted pyrazines has yielded pteridines, *e.g.*, 2 : 4-dihydroxypteridine (Gabriel and Sohn, *Ber.*, 1907, **40**, 4857) and 4-hydroxy- and 4-mercapto-pteridines (Albert, Brown, and Cheeseman, *J.*, 1951, 474) but the scope of the method is severely limited. Pteridines of known structure have been synthesised by Boon, Jones, and Ramage (*J.*, 1951, 96), Boon and Jones (*ibid.*, 591), by Polonovski and Jérome (*Compt. rend.*, 1950, **230**, 392), and by Polonovski, Pesson, and Puister (*ibid.*, 2205) by reduction of α-(5-nitro-4-pyrimidylamino)acetic esters (I; R″ = OEt) and α-(5-nitro-4-pyrimidylamino)-ketones (I; R″ = alkyl or aryl), followed by ring closure; Boon and Leigh (*J.*, 1951, 1497) later developed this method by substituting a phenylazo- for the nitro-group in the pyrimidine moiety.

None of these methods could conveniently, if at all, lead to the required 6- or 7-aminopteridines but a convenient route was found in an extension of the reaction between 4-amino-5-nitrosopyrimidines and ketomethylene compounds, which, by the loss of water between the nitroso- and methylene and the amino- and keto-groups, yields pteridines of unequivocal structure (Timmis, *Nature*, 1949, **164**, 139). This extension involves the condensation of a 4-amino-5-nitrosopyrimidine (II) with an arylacetonitrile with the loss of one mol. of water between the methylene and the nitroso-group. By using an arylacetyl chloride instead of the nitrile corresponding 7-hydroxy-pteridines were obtained which were required for biological comparison.

The 4-amino-5-nitrosopyrimidines required for these condensations were prepared by

the conventional treatment of the appropriate 4-aminopyrimidine with nitrous acid. Since this reaction does not take place unless there are polar groups in the 4- and the 6-position of the pyrimidine ring, the scope of the new pteridine synthesis would be somewhat restricted but for the fact that it has already been shown (Bayer and Co., D.R.-P. 206,453; *Zentr.*, 1909, I, 806) that cyano(hydroxyimino)acetic ester can react with, *e.g.*, guanidine to yield 2 : 4-diamino-6-hydroxy-5-nitrosopyrimidine, and it seems likely that 4-amino-5-nitrosopyrimidines unsubstituted in the 6-position, or substituted by alkyl groups, could be analogously prepared.

Initial attempts to prepare the pteridines (III; R = R′ = NH_2, R″ = Ar) from 2 : 4 : 6-triamino-5-nitrosopyrimidine (II; R = R′ = NH_2) and arylacetonitriles in acetic acid in the presence of anhydrous sodium acetate were only successful when *p*-nitrophenylacetonitrile was used, the compound (III; R = R′ = NH_2, R″ = *p*-NO_2·C_6H_4) being obtained; from experiments with phenylacetonitrile and *p*-methoxyphenylacetonitrile no pteridine was isolated. In the absence of the nitro- or other strongly electron-attracting group in the *para*-position of the phenyl group, it was thought that more strongly basic



catalysts might be effective and this was proved to be the case by the ready synthesis of a series of 7-aminopteridines when the reaction was catalysed by sodium ethoxide in boiling ethanol, sodium 2-ethoxyethoxide in boiling 2-ethoxyethanol, or sodium 2-hydroxyethoxide in boiling ethylene glycol. Ethylene glycol or 2-ethoxyethanol were necessary solvents when the less soluble nitrosopyrimidines were used. Examples of the series are: 2 : 4 : 7-triamino-6-phenyl (III; R = R′ = NH_2, R″ = Ph), 2 : 4 : 7-triamino-6-α-thienyl-, 2 : 4 : 7-triamino-6-α-naphthyl-, 7-amino-2 : 6-diphenyl-, 4-hydroxy-, 7-amino-4-hydroxy-2-methylthio-6-phenyl-, 7-amino-4-hydroxy-2-methyl-6-phenyl-, and 2 : 7-diamino-4-hydroxy-6-phenyl-pteridine.

Evidence for an ortho-effect of the reaction is suggested by the cases where the *o*- and *p*-isomers of chlorophenylacetonitrile, ethoxyphenylacetonitrile, and nitrophenylacetonitrile were condensed with 2 : 4 : 6-triamino-5-nitrosopyrimidine (II; R = R′ = NH_2). In the first two cases, a considerably slower reaction was observed for the *ortho*- than for the *para*-substituted nitriles and in the third case condensation of the *ortho*-isomer was inappreciable even in boiling 2-ethoxyethanol.

Since Barrow and Thorneycroft (*J.*, 1939, 769) isolated the oxide (IV) as a by-product of the reaction of *p*-nitrosodimethylaniline with phenylacetonitrile we have looked, but without success, for pteridine *N*-oxides (V) as by-products of our reaction, since these would have had considerable potential biological interest.

The reaction of 4 : 6-diamino-5-nitroso-2-thiopyrimidine (II; R = SH, R′ = NH_2) with phenylacetonitrile in ethanol containing sodium ethoxide yielded in addition to 4 : 7-diamino-6-phenyl-2-mercaptopteridine (III; R = SH, R′ = NH_2, R″ = Ph) a product which gave correct analytical results for 4 : 7-diamino-2-ethoxy-6-phenylpteridine (III; R = OEt, R′ = NH_2, R″ = Ph). This structure is supported by the close similarity of its ultra-violet absorption spectrum with those of 2 : 4 : 7-triamino-, 4 : 7-diamino-, and 4 : 7-diamino-2-methylthio-6-phenylpteridine.

The 2 : 4 : 7-triamino-6-arylpteridines were conveniently characterised as their triacetyl and the 4 : 7-diamino-2-methylthio- and -2-ethylthio-6-phenylpteridines as their diacetyl derivatives. The pteridines were further characterised by means of their ultra-violet spectra which were also used as criteria of purity where a reliable melting point was not observed.

6-Aryl-7-hydroxypteridines have been obtained by condensation of 4-amino-5-nitrosopyrimidines with arylacetyl chlorides; *e.g.*, phenylacetyl chloride and 2 : 4 : 6-triamino-5-nitrosopyrimidine at 140° gave 2 : 4-diamino-7-hydroxy-6-phenylpteridine, which was also

the major product from phenylglyoxylic acid and a salt of 2 : 4 : 5 : 6-tetra-aminopyrimidine in water at pH 5. When this reaction was carried out in 10% hydrochloric acid solution about 60% of the total product was the 7- and 40% the 6-hydroxy-isomer. The latter compound is readily soluble in dilute ammonia solution, whereas the former is not, indicating that the hydroxyl group in the 6-position is more acidic than that in the 7-position. The ultra-violet absorption spectra of the two compounds are markedly different. Elion, Hitchings, and Russell (*J. Amer. Chem. Soc.*, 1950, **72**, 78) have found that, generally, the 6-alkyl-7-hydroxy-isomer is the major product when a similar reaction with aliphatic keto-acids is carried out at pH 5, and a greater proportion of the 6-hydroxy-isomer is formed in strongly acid solution.

p-Nitrophenylacetyl chloride and *p*-methoxyphenylacetyl chloride with 2 : 4 : 6-triamino-5-nitrosopyrimidine also gave the corresponding pteridines.

As the scope of this reaction appears to be limited by the drastic conditions required and the consequent formation of by-products, attempts were made to condense ethyl phenylacetate and phenylacetamide with 2 : 4 : 6-triamino-5-nitrosopyrimidine, but in no case was the required 2 : 4-diamino-7-hydroxy-6-phenylpteridine obtained.

Conversion of 2-alkylthiopyrimidines into hydroxy-compounds is well known (Lythgoe, *Quart. Reviews*, 1949, **3**, 197; Johnson and Hahn, *Chem. Reviews*, 1933, **13**, 193) and we have now obtained 2-hydroxypteridines by the removal of the 2-methylthio-group from 2-methylthiopteridines on mild acid hydrolysis. Thus, 4 : 7-diamino- and 7-amino-4-hydroxy-2-methylthio-6-phenylpteridine in boiling 10% hydrochloric acid afforded 4 : 7-diamino-2-hydroxy- and 7-amino-2 : 4-dihydroxy-6-phenylpteridine respectively. This method provides the best route to 2-hydroxypteridines, since condensation of 4-amino-5-nitrosopyrimidines and arylacetonitriles does not occur readily when a 2-hydroxy-group is present.

Polonovski, Vieillefosse, and Pesson (*Bull. Soc. chim.*, 1945, **12**, 78) converted 4-hydroxy- and 6 : 7-diphenyl-4-hydroxy-2-mercaptopteridine into the corresponding 2-ethylthio-derivatives by treatment with ethyl bromide in alcoholic alkali. Similarly we have converted 4 : 7-diamino-6-phenyl-2-mercaptopteridine by ethyl bromide into 4 : 7-diamino-2-ethylthio-6-phenylpteridine which was identical with the synthetic material.

Hydrolysis of 2 : 4 : 7-triamino-6-phenylpteridine with 5N-hydrochloric acid yielded a mixture from which 2 : 4-diamino-7-hydroxy-6-phenylpteridine and a product having the spectrum of 2 : 7-diamino-4-hydroxy-6-phenylpteridine was isolated. The triaminopteridine was recovered unchanged on treatment with nitrous acid and thus behaved similarly to the 2 : 4-diaminopteridines (Taylor and Cain, *J. Amer. Chem. Soc.*, 1949, **71**,

Absorption spectra of 2 : 4 : 7-*triaminopteridines* (III; R = R′ = NH_2) *in* 4·5% *formic acid.*

R″	Maxima		Minima		Shoulder	
	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε
Ph	356	21,000	306	3250	281	7050
	257	15,250				
o-EtO·C_6H_4	352	21,400	301	3450	276	8850
	256	16,900				
m-EtO·C_6H_4	358	21,400	307	3750	286	7200
	259	15,650				
p-EtO·C_6H_4	364	21,400	313	4400	287	8000
	250	19,700				
p-NO_2·C_6H_4	368	22,470	300	6800		
	258	21,150				
α-Thienyl	377	18,900	324	3800		
	302	8,050	287	7600		
	260	15,700				
o-Cl·C_6H_4	351	20,550	301	2470	280	6350
	259	15,100				
m-Cl·C_6H_4	358	21,400	309	3250	285	7200
	254	15,250				
p-Cl·C_6H_4	359	21,700	309	3200	285	7550
	251	16,800				
4 : 7-Diamino-2-ethoxy(?)-6-phenylpteridine	354	19,400	306	3800	280	7200
	258	14,500				

Absorption spectra of 7-*aminopteridines* (III; R″ = Ph) *in acid and alkaline solution.*

		4·5% HCO_2H solution				0·1N-NaOH solution			
		Maxima		Minima		Maxima		Minima	
R	R′	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε	(λ (mμ)	ε
MeS	NH_2	363	22,900	311	3,400				
		267	21,500						
EtS	NH_2	364	23,100	311	3,600				
		266	20,700						
NH_2	OH	347	16,300	307	5,500	365	18,000	312	2,600
		287	9,900	260	3,950	267	12,800	253	10,800
						228	35,600		
Me	OH					352	15,800	295	3,100
						263	13,500	254	11,800
						231	24,300		
H	NH_2	356	16,200	309	3,850				
		290	5,150	286	5,100				
		262	16,650						
H	OH					352	14,200	290	3,000
						262	12,400	255	11,700
						230	23,050		
SH	NH_2	375	24,400	333	8,600	383	20,450	328	4,100
		311	15,200	290	11,200	283	20,750	263	12,800
		271	21,900	259	16,300	239	26,120	222	16,200
		249	18,750						
OH	NH_2	355	19,400	312	5,400	369	17,100	314	2,800
		292	10,300	265	5,000	273	13,400	255	10,400
						288	33,900		
MeS	OH					357	15,600	305	3,000
						264	13,100	251	10,500
						288	25,700		

Absorption spectra of 2 : 4-*diamino*-7-*hydroxypteridines* (VIII; R = R′ = NH_2).

	4·5% HCO_2H solution				0·1N-NaOH solution			
	Maxima		Minima		Maxima		Minima	
R″	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε
Ph	362	19,650	310	4,000	362	19,900	324	9,400
	267	12,100	256	11,000	306	14,000	271	3,950
	229	43,150			217	34,800		
p-MeO·C_6H_4	367	20,700	314	4,500				
	272	13,400	257	11,850				
	228	44,700						
p-NO_2·C_6H_4	394	19,300	294	6,350				
	249	20,700 *						
	224	37,700						

* Shoulder.

2538) in which the 4-amino-group was removed by hydrolysis with 5N-hydrochloric acid but neither group was affected by nitrous acid.

The results of the biological tests were disappointing since none of the anti-folic acid activities approached that found for 2 : 4-diamino-6 : 7-diphenylpteridine (Daniel *et al.*, *loc. cit.*). The two most active compounds 2 : 4 : 7-triamino-6-*p*-chlorophenyl- and -6-α-thienyl-pteridine had approximately one hundredth of the activity of the diphenylpteridine (H. Proom, personal communication).

Ultra-violet absorption spectra, which have been determined (where possible) in acid and alkaline solution, are shown in the Tables. Owing to the insolubility of most of the compounds in dilute hydrochloric acid, solutions in 4·5% formic acid were used which were prepared by dissolving the substance in 90% formic acid and diluting it with water.

The spectra of 2 : 4-diamino-7-hydroxy-6-phenylpteridine and 2 : 4-diamino-6-hydroxy-7-phenylpteridine in both acid and alkaline media resemble those of the corresponding methylpteridines (Elion, Hitchings, and Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 78). The presence of a 6- or 7-phenyl group has, as expected (because of the extra conjugation of the aryl group with the pteridine nucleus), increased the intensity of the bands, which are also shifted to longer wave-lengths. However a close analogy between the methyl and the

phenyl isomers is shown in the changes brought about by using alkaline instead of acid solutions (see Table).

2 : 4-Diaminopteridine	0·1N-Acid λ (mμ)	0·1N-Acid ε	0·1N-Alkali λ (mμ)	0·1N-Alkali ε
7-Hydroxy-6-methyl	333	15,000	340	15,000
7-Hydroxy-6-phenyl	362	19,800	362	19,600
6-Hydroxy-7-methyl	350	7,100	385	6,100
6-Hydroxy-7-phenyl	380	17,400	409	11,200

The long wave-length band undergoes little change in the series of 7-aminopteridines, with a change of substituents in the 2-, 4-, or 6-position but the introduction of a 2-hydroxy- or 2-thio-group causes a marked change in the short wave-length band. It is also the short wave-length band which is most affected by a change of solvent: the long wave-length band is only shifted to a longer wave-length in changing from acid to alkaline solution but is relatively unchanged in intensity.

The spectrum of the alkali-insoluble sulphur-free material from the condensation of 4 : 6-diamino-5-nitroso-2-thiopyrimidine and phenylacetonitrile, in acid solution more closely resembles the spectra of 4 : 7-diamino-6-phenylpteridines with amino-, hydrogen, or 2-methylthio-substituents in the 2 position than those with a hydroxyl or thio-group in this position. Combined with the analytical figures the spectral data given in the first Table indicate that this compound is 4 : 7-diamino-2-ethoxy-6-phenylpteridine.

Experimental

M. p.s were determined in an electrically heated copper block. Absorption spectra were measured with a Beckman spectrophotometer. Fluorescence was observed in ultra-violet light from a Hanovia lamp. Analyses of compounds marked * are tabulated below. Analytical samples were dried *in vacuo* at temperatures stated in parentheses.

4-*Chlorobenzyl Bromide.*—*p*-Chlorotoluene (31·6 g.) was dissolved in dry carbon tetrachloride (150 c.c.), finely powdered *N*-bromosuccinimide (53·5 g.) and benzoyl peroxide (0·1 g.) were added, and the mixture was refluxed for 5—6 hr. The succinimide was filtered off and washed

2 : 4 : 7-*Triamino*-6-*arylpteridines* (III; R = R′ = NH_2).

R″	Cryst. form and solvent *		M. p.†	Formula	Found (%)‡ C	H	N	Required (%) C	H	N
Ph	Yellow plates	B	316°	$C_{12}H_{11}N_7$	57·2	4·7	39·5	56·9	4·4	38·7
p-NO_2·C_6H_4	Orange prisms	F	356—358	$C_{12}H_{10}O_2N_8$	48·3	3·8	37·2	48·3	3·4	37·6
p-MeO·C_6H_4	Yellow plates	A	328	$C_{13}H_{13}ON_7$	55·6	4·9	34·6	55·1	4·6	34·6
p-EtO·C_6H_4	Yellow needles	A	348—350	$C_{14}H_{15}ON_7$	56·4	4·9	32·65	56·6	5·09	33·0
m-MeO·C_6H_4	Yellow needles	F	330	$C_{13}H_{13}ON_7$	55·4	5·0	35·1	55·1	4·6	34·6
m-EtO·C_6H_4	Yellow needles	A	310—312	$C_{14}H_{15}ON_7$	56·3	4·9	32·9	56·6	5·1	33·0
o-MeO·C_6H_4	Orange-yellow rods	P	334	$C_{13}H_{13}ON_7$	54·4	4·3	36·0	55·1	4·6	34·6
o-EtO·C_6H_4	Yellow prisms	P	308	$C_{14}H_{15}ON_7$	56·7	5·3	33·8	56·6	5·1	33·0
p-Cl·C_6H_4	Lemon-yellow prisms	A	378—380	$C_{12}H_{10}N_7Cl$	50·2	3·5	34·0	50·5	3·5	34·1
m-Cl·C_6H_4	Yellow prisms	A	353	$C_{12}H_{10}N_7Cl$	50·3	4·1	34·3	50·5	3·5	34·1
o-Cl·C_6H_4	Pale yellow rods	DA	342	$C_{12}H_{10}N_7Cl$	50·1	4·2	34·1	50·5	3·5	34·1
p-F·C_6H_4	Yellow needles	A	362	$C_{12}H_{10}N_7F$	53·2	4·5	34·9	53·1	3·7	36·2
m-NO_2·C_6H_4	Yellow needles	F	360	$C_{12}H_{10}O_2N_8$	48·5	5·0	37·75	48·3	3·4	37·6
α-Thienyl	Deep yellow prisms	A	356—358	$C_{10}H_9N_7S$	46·7	3·8	37·8	46·3	3·5	37·8
α-Naphthyl	Yellow needles	A	384	$C_{16}H_{13}N_7$	63·7	4·5	32·0	63·4	4·3	32·3

* Solvents were: B, *n*-butanol; A, glacial acetic acid; DA, aqueous dimethylformamide; F, 80% formic acid; P, precipitation from a hot dilute acid solution with dilute ammonia; D, dimethyl formamide; E, ethanol.

† With decomp., except the first. ‡ Dried at 170° *in vacuo*.

with a little dry carbon tetrachloride. The solvent was evaporated from the combined filtrate and washings, and the residue was distilled *in vacuo*, 4-chlorobenzyl bromide (37·25 g.), b. p. 122—126°/20 mm., being obtained.

3-Chlorobenzyl bromide, b. p. 115—119°/20 mm., and 3-nitrobenzyl bromide, m. p. 55°, were obtained in good yield by the same method.

2 : 4 : 7-*Triamino*-6-*phenylpteridine.*—Sodium (0·45 g.) was dissolved in hot dry 2-ethoxyethanol (180 c.c.), and 2 : 4 : 6-triamino-5-nitrosopyrimidine (2·25 g.) was added, followed by redistilled phenylacetonitrile (2·1 g.). After 2 hours' refluxing the dark brown solution, which showed an intense blue fluorescence in ultra-violet light, was evaporated to dryness *in vacuo*, the

residue dissolved in hot 10% hydrochloric acid, and the solution treated with charcoal and filtered. The yellow filtrate was neutralised with 10% aqueous ammonia and allowed to cool, and the yellow base collected. Several crystallisations from *n*-butanol gave 2 : 4 : 7-triamino-6-phenylpteridine * (2 g., 55%) as yellow plates, m. p. 316°.

2 : 4 : 7-*Triamino*-6-p-*nitrophenylpteridine*.—2 : 4 : 6-Triamino-5-nitrosopyrimidine (0·75 g.), freshly fused sodium acetate (0·5 g.), and *p*-nitrophenylacetonitrile (0·9 g.) were refluxed in glacial acetic acid (40 c.c.) for 20 hr. The solution was filtered hot and, on cooling, gave a mixture apparently containing unchanged nitroso-compound. The product, on trituration with 10% hydrochloric acid, left a yellow solid, which was extracted with 10% ammonia solution. Crystallisation from 80% formic acid gave 2 : 4 : 7-triamino-6-*p*-nitrophenylpteridine * (0·85 g.) as orange prisms, m. p. 356—358° (decomp.).

Other 2 : 4 : 7-*Triamino*-6-*arylpteridines* (III; R = R′ = NH_2).—Sodium (0·01 mol.) was dissolved in dry 2-ethoxyethanol (60 c.c.), and 2 : 4 : 6-triamino-5-nitrosopyrimidine (1·50 g.) and the appropriate arylacetonitrile (0·012 mol.) were added to the hot solution which was then refluxed for 1—2 hr. At this stage the pteridine was usually precipitated and the mixture was cooled and filtered, and the product recrystallised from the appropriate solvent. The properties and analyses of these compounds are tabulated (p. 2891).

2 : 4 : 7-*Triacetamido*-6-*arylpteridines*.—These derivatives were prepared by refluxing the base with acetic anhydride and are described in the annexed Table.

Acetyl derivatives.

	Cryst. form and solvent *	M. p.	Formula	Found (%) N	Required (%) N
2 : 4 : 7-*Triacetamidopteridine derivative*					
6-Phenyl	Lemon-yellow needles A	282—284°	$C_{18}H_{17}O_3N_7$	26·1	25·85
6-*p*-Nitrophenyl	Yellow needles D	315—316	$C_{18}H_{16}O_5N_8$	26·6	26·4
6-*p*-Methoxyphenyl	Yellow needles D	272	$C_{19}H_{19}O_4N_7$	24·3	23·95
6-*p*-Ethoxyphenyl	Yellow needles D	230	$C_{20}H_{21}O_4N_7$	23·7	23·2
6-*p*-Chlorophenyl	Yellow prisms D	350	$C_{18}H_{16}O_3N_7Cl$	24·0	23·7
4 : 7-*Diacetamido*-6-*phenylpteridines*					
2-Methylthio-6-phenyl	Yellow needles E	230	$C_{17}H_{16}O_2N_6S$	22·7	22·8
2-Ethylthio-6-phenyl	Yellow needles E	209—210	$C_{18}H_{18}O_2N_6S$	21·2	22·0

* Footnote as preceding Table.

4 : 7-*Diamino*-2-*methylthio*-6-*phenylpteridine*.—4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine (0·5 g.) and phenylacetonitrile (0·35 g.) were added to a solution of sodium (0·1 g.) in dry ethanol (60 c.c.), and the mixture was refluxed for 1 hr. When separation of the crystalline solid was complete the mixture was cooled, the solid collected, dissolved in cold 5% hydrochloric acid, and the solution treated with charcoal and neutralised with 2N-ammonia. The dried precipitate after several crystallisations from *n*-butanol gave pale yellow plates of 4 : 7-*diamino*-2-*methylthio*-6-*phenylpteridine*, m. p. 306° (pale yellow needles were obtained if the solution cooled slowly) [Found (135°): C, 55·2; H, 4·16; N, 29·6. $C_{13}H_{12}N_6S$ requires C, 55·0; H, 4·23; N, 29·5%].

4 : 7-*Diamino*-2-*ethylthio*-6-*phenylpteridine*.—4 : 6-Diamino-2-ethylthio-5-nitrosopyrimidine (0·5 g.) and phenylacetonitrile (0·35 g.) were condensed in ethanol (60 c.c.) containing dissolved sodium (0·1 g.) as above, and the product, after purification by dissolution in 5% hydrochloric acid and precipitation with dilute ammonia solution, crystallised from *n*-butanol in lemon-yellow plates, m. p. 272—274° [Found (135°): C, 56·7; H, 4·8; N, 27·85. $C_{14}H_{14}N_6S$ requires C, 56·4; H, 4·7; N, 28·2%].

2 : 7-*Diamino*-4-*hydroxy*-6-*phenylpteridine*.—To a solution from sodium (0·5 g.) in dry ethylene glycol (45 c.c.) were added 2 : 4-diamino-6-hydroxy-5-nitrosopyrimidine (0·75 g.) and phenylacetonitrile (0·7 g.), and the mixture was refluxed for 7 hr. The solvent was removed *in vacuo*, the residue dissolved in hot water, and the solution treated with charcoal and neutralised with acetic acid, yielding a brown amorphous precipitate. Crystallised from 10% hydrochloric acid (charcoal), this gave the *hydrochloride* (0·3 g.). Two further crystallisations from 2% hydrochloric acid gave a pure specimen as light buff needles [Found (170°): C, 49·3; H, 4·35; N, 29·0. $C_{12}H_{10}ON_6$,HCl requires C, 49·6; H, 3·8; N, 29·0%].

The *base*, prepared from the pure hydrochloride by treatment with hot dilute ammonia

solution, was purified by precipitation from hot 0·1N-sodium hydroxide with N-acetic acid as a buff solid which decomposed above 350° [Found (170°): C, 53·5; H, 5·1; N, 31·0. $C_{12}H_{10}ON_6,H_2O$ requires C, 52·9; H, 4·45; N, 30·8%]. Longer drying then 3 hr. gave variable analytical results indicating 0—1 mol. of water of crystallisation.

7-Amino-4-hydroxy-2-methyl-6-phenylpteridine.—When 4-amino-6-hydroxy-2-methyl-5-nitrosopyrimidine and phenylacetonitrile were condensed in 2-ethoxyethanol containing sodium 2-ethoxyethoxide, a colourless solid was obtained. Crystallisation from 2% hydrochloric acid gave needles of the *hydrochloride* [Found (100°): C, 53·3; H, 4·4; N, 23·9. $C_{13}H_{11}ON_5,HCl$ requires C, 53·9; H, 4·18; N, 24·2%].

The *base*, prepared by dissolving the hydrochloride in hot 0·1N-sodium hydroxide and adding the theoretical amount of N-acetic acid, separated as colourless plates, which decomposed above 350° [Found (135°): C, 61·6; H, 4·4; N, 27·9. $C_{15}H_{11}ON_5$ requires C, 61·6; H, 4·4; N, 27·7%].

4 : 7-Diamino-6-phenylpteridine.—The crude product from the reaction of 4 : 6-diamino-5-nitrosopyrimidine with phenylacetonitrile was purified by dissolution in acid and precipitation with alkali. 4 : 7-*Diamino-6-phenylpteridine* crystallised from *n*-butanol in pale yellow prisms, m. p. 340° (decomp.) [Found (135°): C, 60·5; H, 4·4; N, 35·1. $C_{12}H_{10}N_6$ requires C, 60·5; H, 4·25; N, 36·3%].

7-Amino-4-hydroxy-6-phenylpteridine, similarly prepared from 4-amino-6-hydroxy-5-nitrosopyrimidine and purified by dissolving it in 0·1N-sodium hydroxide and adding the theoretical quantity of 0·1N-acetic acid to the boiling solution, separated as buff plates which decomposed without melting above 350° [Found (170°): C, 60·2; H, 4·1; N, 30·4. $C_{12}H_9ON_5$ requires C, 60·2; H, 3·8; N, 29·3%].

7-Amino-4-hydroxy-2 : 6-diphenylpteridine.—4-Amino-6-hydroxy-5-nitroso-2-phenylpyrimidine (0·54 g.) and phenylacetonitrile (0·35 g.) were condensed in 2-ethoxyethanol (60 c.c.) containing dissolved sodium (0·13 g.). The solid (0·35 g.) obtained by evaporation to dryness *in vacuo* and trituration with 10% acetic acid was dissolved in 5% potassium hydroxide solution and neutralised with dilute acetic acid, whereupon 7-*amino*-4-*hydroxy*-2 : 6-*diphenylpteridine* separated as a pale yellow solid which rapidly decomposed above 400° [Found (170° over P_2O_5): C, 67·2; H, 4·25; N, 22·1. $C_{18}H_{13}ON_5$ requires C, 67·3; H, 4·1; N, 21·8%].

4 : 7-Diamino-2-mercapto-6-phenylpteridine.—A solution of 4 : 6-diamino-5-nitroso-2-thiopyrimidine (0·84 g.) and phenylacetonitrile (0·7 g.) in ethanol (150 c.c.) in which sodium (0·23 g.) had been dissolved was refluxed for 4 hr., evaporated to small bulk, diluted with one volume of water, and cooled. The precipitated alkali-insoluble material A (0·2 g.) was purified by dissolution in hot 10% hydrochloric acid solution, treatment with charcoal, and neutralisation of the hot filtrate with ammonia, followed by several crystallisations from *n*-butanol from which it separated as pale yellow prisms, m. p. 290° (decomp.) [Found (135°): C, 59·3; H, 4·6; N, 30·2. 4 : 7-*Diamino-2-ethoxy-6-phenylpteridine*, $C_{14}H_{14}ON_6$, requires C, 59·6; H, 5·0; N, 29·8%]. Solutions of this substance had an intense blue fluorescence in ultra-violet light.

The filtrate from A was treated with charcoal when hot, and neutralised with dilute acetic acid. The yellow precipitate was dissolved in hot 0·2N-sodium hydroxide solution; the solution was filtered and neutralised with the theoretical amount of dilute acetic acid. After cooling, the yellow precipitate was dissolved in hot 10% hydrochloric acid and this was neutralised with dilute ammonia solution, to yield 4 : 7-*diamino-2-mercapto-6-phenylpteridine* (0·65 g.) as deep yellow prisms, which decomposed above 310° [Found (170° over P_2O_5): C, 53·5; H, 4·0; N, 31·1. $C_{12}H_{10}N_6S$ requires C, 53·3; H, 3·7; N, 31·1%]. This substance has a dull blue fluorescence in both acid and alkaline solution under ultra-violet light.

4 : 7-Diamino-2-hydroxy-6-phenylpteridine.—To a solution of sodium (0·23 g.) in ethylene glycol (60 c.c.) was added 4 : 6-diamino-2-hydroxy-5-nitrosopyrimidine and phenylacetonitrile (0·7 g.), the mixture was refluxed for 1 hr. and the solvent removed *in vacuo*. The residue was dissolved and purified by alkali, charcoal, and acid as usual, then dissolved in a little 100% formic acid, diluted with one volume of water, treated with charcoal, and neutralised with dilute ammonia solution when still hot. The precipitated solid was further purified by dissolution in 0·1N-sodium hydroxide and reprecipitation with the theoretical quantity of dilute acetic acid solution, yielding 4 : 7-*diamino-2-hydroxy-6-phenylpteridine* as a yellow solid [Found (170° over P_2O_5): N, 32·4. $C_{12}H_{10}ON_6$ requires N, 33·1%]. The ultra-violet absorption spectrum of this material showed its identity with the pteridine obtained by the dilute acid hydrolysis of 4 : 7-diamino-2-methylthio-6-phenylpteridine.

2 : 4-Diamino-7-hydroxy-6-phenylpteridine.—2 : 4 : 6-Triamino-5-nitrosopyrimidine (1 g.) was stirred with phenylacetyl chloride (10 c.c.) and heated to 140°, reaction being complete

when no more hydrogen chloride was evolved (about 10 min.). The dark brown solution, cooled and diluted with ether, yielded a light brown precipitate which, after being washed with ether, was stirred with hot dilute ammonia solution to liberate the free base. This after several crystallisations from glacial acetic acid gave yellow prisms of 2 : 4-*diamino*-7-*hydroxy*-6-*phenylpteridine* (1 g.), m. p. 406—408° (decomp.) [Found (170° over P_2O_5) : C, 56·5; H, 3·8; N, 33·2. $C_{12}H_{10}ON_6$ requires C, 56·7; H, 4·0; N, 33·1%]. This substance had an intense blue fluorescence under ultra-violet light in both acid and alkaline solution.

2 : 4-*Diamino*-7-*hydroxy*-6-p-*nitrophenylpteridine*.—2 : 4 : 6-Triamino-5-nitrosopyrimidine was intimately ground with *p*-nitrophenylacetyl chloride (5 g.) and slowly heated to 140° as above. After similar treatment the crude base (1·3 g.) was obtained as an orange-brown solid. The solid was repeatedly extracted with hot dilute ammonia solution, the orange solution evaporated to small bulk *in vacuo*, and the orange precipitate crystallised from 80% formic acid, to yield 2 : 4-*diamino*-7-*hydroxy*-6-p-*nitrophenylpteridine* as orange-yellow needles which became deep red at 170° *in vacuo*. The substance slowly decomposed above 400° (Found : C, 47·9; H, 3·4; N, 32·5. $C_{12}H_9O_3N_7$ requires C, 48·2; H, 3·8; N, 32·8%). Solutions of this material in acid or alkali had only a weak green fluorescence in ultra-violet light.

2 : 4-*Diamino*-7-*hydroxy*-6-p-*methoxyphenylpteridine*.—Reaction of 2 : 4 : 6-triamino-5-nitrosopyrimidine (1 g.) and *p*-methoxyphenylacetyl chloride (7 c.c.) at 140° gave 1·3 g. of crude product, purified by extraction with 1 l. of 10% potassium hydroxide solution, acidification of the extract with glacial acetic acid, and several crystallisations from dimethylformamide. 2 : 4-*Diamino*-7-*hydroxy*-6-p-*methoxyphenylpteridine* crystallised as yellow prisms which decomposed above 350° [Found (170° over P_2O_5) : C, 55·3; H, 4·7; N, 29·4. $C_{13}H_{12}O_2N_6$ requires C, 54·9; H, 4·3; N, 29·6%].

Condensation of 2 : 4 : 5 : 6-*Tetra-aminopyrimidine Hydrochloride with Phenylglyoxylic Acid*.—(a) *At* pH 5. 2 : 4 : 5 : 6-Tetra-aminopyrimidine hydrochloride (0·19 g.), sodium acetate (0·45 g.), and phenylglyoxylic acid (0·15 g.), dissolved in warm water (10 c.c.), were refluxed for 10 min. and yielded a precipitate which crystallised from acetic acid as yellow prisms, (0·18 g.), m. p. 406—408° alone or admixed with 2 : 4-diamino-7-hydroxy-6-phenylpteridine obtained by the condensation of 2 : 4 : 6-triamino-5-nitrosopyrimidine and phenylacetyl chloride. The ultra-violet absorption spectra of the samples were identical.

(b) *In acid solution*. 2 : 4 : 5 : 6-Tetra-aminopyrimidine (0·9 g.) and phenylglyoxylic acid (0·7 g.) in 10% hydrochloric acid (25 c.c.) and ethanol (15 c.c.) were refluxed for 1 hr. The precipitate was collected and the filtrate evaporated to dryness; the combined solids (1·25 g.) were extracted with hot 10% ammonia solution (3 × 75 c.c.), to leave 2 : 4-diamino-7-hydroxy-6-phenylpteridine (0·65 g.) which crystallised in yellow prisms, m. p. 406—408°, identical in m. p. and other physical properties with the preceding product. The ammonia extract, on evaporation to small bulk, left a deep orange solid (0·5 g.) which, in contrast to 2 : 4-diamino-7-hydroxy-6-phenylpteridine, had in acid solution a deep green fluorescence in ultra-violet light. This solid, crystallised several times from water, yielded golden needles of 2 : 4-*diamino*-6-*hydroxy*-7-*phenylpteridine* which decomposed above 310° [Found (170° over P_2O_5) : C, 57·0; H, 4·2; N, 32·7. $C_{12}H_{10}ON_6$ requires C, 56·7; H, 4·0; N, 33·1%].

Hydrolysis of 4 : 7-*Diamino*-2-*methylthio*-6-*phenylpteridine*.—The 2-methylthio-compound (0·1 g.) was refluxed with 10% hydrochloric acid (15 c.c.) until no more methanethiol was evolved. The solution was cooled, and the yellow precipitate was collected, dissolved in hot N-sodium hydroxide, treated with charcoal, heated to boiling, and carefully neutralised with dilute acetic acid. 4 : 7-Diamino-2-hydroxy-6-phenylpteridine (80 mg.) separated as a pale yellow powder, decomp. > 320° [Found (170° over P_2O_5) : C, 56·6; H, 4·4; N, 32·5%], having an absorption spectrum identical with that of a synthetic specimen.

Hydrolysis of 7-*Amino*-4-*hydroxy*-2-*methylthio*-6-*phenylpteridine*.—The pteridine (0·1 g.) was boiled with 2N-hydrochloric acid (15 c.c.) until all the methanethiol had been evolved. After cooling, the precipitate was collected and dissolved in hot 0·5N-sodium hydroxide (20 c.c.), and the product purified and isolated as in the preceding experiment, to yield pale yellow rhombs of 7-*amino*-2 : 4-*dihydroxy*-6-*phenylpteridine*, decomp. > 330° [Found (170° over P_2O_5) : C, 56·6; H, 3·0; N, 26·2. $C_{12}H_9O_2N_5$ requires C, 56·6; H, 2·8; N, 27·4%].

Hydrolysis of 2 : 4 : 7-*Triamino*-6-*phenylpteridine*.—The triamine (0·2 g.) was refluxed with 5N-hydrochloric acid (30 c.c.) for 1 hr. and the solid (A) collected from the hot solution. On cooling, another solid (B) separated.

Solid (B) was dissolved in hot 0·1N-sodium hydroxide, treated with charcoal, and neutralised with dilute acetic acid, and the precipitate was extracted with boiling 10% hydrochloric acid leaving very little residue. After cooling to 30° the amorphous precipitate was filtered off and

the filtrate was treated with charcoal. During several hours at room temperature the colourless solution deposited slender needles of 2 : 7-diamino-4-hydroxy-6-phenylpteridine hydrochloride (0·13 g.), identical in ultra-violet absorption with the hydroxypteridine obtained by direct synthesis from 2-amino-4-hydroxy-5-nitrosopyrimidine.

Solid (A), after purification by precipitation from an alkaline solution with acid, was shown to be 2 : 4-diamino-7-hydroxy-6-phenylpteridine by comparison of its ultra-violet absorption spectrum in 0·1N-sodium hydroxide with that of a synthetic specimen (Found: N, 33·1. $C_{12}H_{10}ON_6$ requires N, 33·8%).

When the triamine (0·2 g.) was boiled for several hours with 10% hydrochloric acid, 0·18—0·19 g. of the starting material was recovered. No alkali-soluble material was obtained.

Ethylation of 4 : 7-*Diamino*-2-*mercapto*-6-*phenylpteridine*.—To a solution of sodium (0·05 g.) in ethanol (25 c.c.) was added the mercaptopteridine (0·1 g.), followed by ethyl bromide (0·1 c.c.). The clear yellow solution was refluxed for 2 hr.; the original dull blue fluorescence in ultra-violet light had changed to a sky-blue fluorescence. The mixture was worked up as described for the synthesis of 4 : 7-diamino-2-ethylthio-6-phenylpteridine, yellow plates, m. p. 272°, being obtained. Comparison of the ultra-violet absorption spectrum of this pteridine with that of 4 : 7-diamino-2-ethylthio-6-phenylpteridine confirmed their identity.

Oxidation of 4 : 7-*Diamino*-2-*mercapto*-6-*phenylpteridine*.—To a solution of the 2-mercapto-compound (0·1 g.) in 0·1N-sodium hydroxide (10 c.c.), was added hydrogen peroxide (5 c.c. of 20-vol.), and the mixture kept at room temperature overnight. The pale yellow solution, acidified with acetic acid, yielded a precipitate which was purified by dissolution in dilute sodium hydroxide solution and reprecipitation with acetic acid. The pale yellow microcrystalline solid showed an absorption spectrum identical with that of 4 : 7-diamino-2-hydroxy-6-phenylpteridine prepared by synthesis.

We thank Professor A. Haddow for his interest and encouragement and record also our indebtedness to the late Professor G. A. R. Kon. We are also very much indebted to Drs. R. N. Beale and E. M. F. Roe for the determination of absorption spectra, and to Mr. H. Proom, Wellcome Research Laboratories, Beckenham, for the micro-biological experiments. We thank Miss K. Chilton for the analyses.

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*The Synthesis of Compounds with Potential Anti-folic Acid Activity. Part II.** 5 : 7 : 9 : 10-*Tetra-aza*-1 : 2-*benzanthracene and Related Compounds.*

By D. G. I. FELTON, T. S. OSDENE, and G. M. TIMMIS.

[Reprint Order No. 5081.]

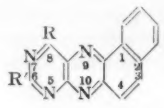
The synthesis is reported of a number of mono- and di-substituted 5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracenes by the fusion of 4-amino-5-nitrosopyrimidines with 2-naphthol. The structures are proved unequivocally by alternative methods of synthesis and interconversions. Starting from 1-nitroso-2-naphthylamine, 2-amino-5 : 6-benzoquinoxaline-3-carbonamide is prepared and this is cyclised by known methods to a number of tetra-azabenzanthracenes. A number of compounds, previously ambiguously orientated, are now allotted unequivocal structures. The reactions and stability of compounds in this series are compared with those of the related pteridine series, and the similarities and differences are commented upon briefly. A number of related compounds are described.

IT has been shown (*J.*, 1954, 2881) that reaction between 2 : 4 : 6-triamino-5-nitrosopyrimidine and *NN*-di-2′-chloroethyl-2-naphthylamine yields 6 : 8-diamino-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = R′ = NH_2) and an excellent method of preparing this compound was found in the fusion of the triaminonitrosopyrimidine with 2-naphthol at 150°. Previous compounds of this series have been prepared by methods which do not

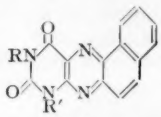
* Part I, preceding paper.

unambiguously define the structures (see *loc. cit.*). The reactions described below, however, lead to the unambiguously oriented series (I). That the products consist of one isomer only has been shown by paper chromatography, using the ascending front technique with butanol–5N-acetic acid as the mobile phase (see Albert, *Quart. Reviews*, 1952, **6**, 197, for leading references to this procedure), and detection by the ultra-violet fluorescence.

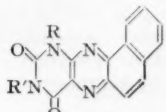
The scope of the fusion reaction was first investigated. Besides **2 : 4 : 6**-triamino-5-nitrosopyrimidine which yields (I; R = R′ = NH_2), **4 : 6**-diamino-2-dimethylamino-5-nitrosopyrimidine gave the analogue (I; R = NH_2, R′ = NMe_2). **2 : 4**-Diamino-6-hydroxy-, **4 : 6**-diamino-2-hydroxy-, and 4-amino-**2 : 6**-dihydroxy-5-nitrosopyrimidine did not react, probably owing to the insolubility of these compounds in molten 2-naphthol, but 4-amino-6-hydroxy-5-nitrosopyrimidine-2-thiol and the corresponding methylthio-compound reacted extremely vigorously to yield charred black masses from which no pure product was isolated. However, smooth reactions occurred between fused 2-naphthol and 4-amino-**1 : 2 : 3 : 6**-tetrahydro-**1 : 3**-dimethyl-5-nitroso-**2 : 6**-dioxopyrimidine, to yield **5 : 6 : 7 : 8**-tetrahydro-**5 : 7**-dimethyl-**6 : 8**-dioxo-**5 : 7 : 9 : 10**-tetra-aza-**1 : 2**-benzanthracene, m. p. 278° (II; R = R′ = Me) and between 2-naphthol and 4-amino-**3 : 6**-dihydro-2-hydroxy-3-methyl-5-nitroso-6-oxopyrimidine to give **5 : 6 : 7 : 8**-tetrahydro-5-methyl-**6 : 8**-dioxotetra-azabenzanthracene, m. p. 390° (II; R = H, R′ = Me).



(I)



(II)



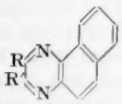
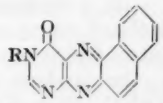
(III)

Kühling (*Ber.*, 1891, **24**, 3029) and Kuhn and Cook (*Ber.*, 1937, **70**, 761) claimed to have prepared (II; R = R′ = Me). From **1 : 2**-diaminonaphthalene hydrochloride and tetramethylalloxantin in boiling water Kühling obtained a product, m. p. 285°, probably a mixture of (II; R = R′ = Me) and (III; R = R′ = Me). He further treated **1 : 2**-diaminonaphthalene hydrochloride with dimethylalloxantin and gave the product, m. p. >300°, the structure (II; R = H, R′ = Me) although clearly he was unable to discriminate between this and (II; R = Me, R′ = H) or (III; R = H, R′ = Me; or R = Me, R′ = H). Kuhn and Cook, on the other hand, treated **1 : 2**-diaminonaphthalene with alloxan following Kühling's procedure (*Ber.*, 1891, **24**, 2363) to obtain either (I; R = R′ = OH) or the **6 : 8 : 9 : 10**-tetra-aza-analogue or a mixture of both; they also treated **1 : 2**-naphthaquinone with **4 : 5**-diamino-**2 : 6**-dihydroxypyrimidine; with diazomethane in ether these products yielded different *NN′*-dimethyl compounds (II and III; R = R′ = Me): that originating from alloxan and diaminonaphthalene had m. p. 258—260°, and the other melted at 308° (decomp.). Very probably the isomer of m. p. 258—260° corresponds to that synthesised by us. But a repetition of Kuhn and Cook's work yielded us an isomer, m. p. 318°, different from (II; R = R′ = Me) and presumably corresponding to their compound, m. p. 308° (decomp.). In the case of the reaction between alloxan and **1 : 2**-diaminonaphthalene, crystallisation of the dihydroxy-compound from acetic acid to single-spot purity on a paper chromatogram, followed by treatment with diazomethane, yielded the pure isomer, m. p. 318°, directly. If the intermediate purification was omitted, or replaced by one precipitation from cold alkali by acid, then fractional crystallisation of the methylated product yielded also a more soluble fraction, which however, did not yield the pure isomer, m. p. 258—260°. Furthermore a paper chromatogram of the crude mixture of products obtained by Kühling's procedure failed to reveal the presence of the dihydroxy-compound (I; R = R′ = OH), and similar investigation of the lower-melting fractions from the diazomethylation of this demonstrated the absence of the dimethyldioxo-compound (II; R = R′ = Me). Dr. A. H. Cook (personal communication) has pointed out to us the effect of impurities upon alloxan condensations and this seems the most reasonable explanation of the discrepancy.

The formulation as (II; R = R′ = Me) of the compound, m. p. 278°, obtained by us has been confirmed by two independent routes.

(*a*) The general reaction for the preparation of 7-aminopteridines (Part I, *loc. cit.*) has been extended by condensing *o*-aminonitroso-compounds with cyanoacetamide and its congeners. This very useful reaction has been employed in the synthesis of numerous fused heterocyclic systems, which will be described later. Thus 1-nitroso-2-naphthylamine and cyanoacetamide condensed in 2-ethoxyethanol in the presence of sodium 2-ethoxyethoxide, yielding 2-amino-5 : 6-benzoquinoxaline-3-carbonamide (IV; R = CO·NH_2, R′ = NH_2), and condensation with cyanoacetic acid or methyl cyanoacetate gave the corresponding 3-carboxylic acid (IV; R = CO_2H, R′ = NH_2). The acid underwent ready thermal decarboxylation to 2-aminobenzoquinoxaline, m. p. 219—220° (IV; R = H, R′ = NH_2). This amine was described but not orientated by Wolf, Beutel, and Stevens (*J. Amer. Chem. Soc.*, 1948, **70**, 2572) who hydrolysed the mixture of dihydroxy-tetra-azabenzanthracenes (benzalloxazines) obtained by Kuhn and Cook (*loc. cit.*) to the aminobenzoquinoxaline carboxylic acids. These were decarboxylated to give a mixture of aminobenzoquinoxalines, separated by fractional crystallisation into two compounds, m. p.s 150—152° and 215—217° respectively. It is now clear that the latter is 2-amino-5 : 6-benzoquinoxaline (IV; R = H, R′ = NH_2), and the former the 3-amino-isomer (IV; R = NH_2, R′ = H). Attempted hydrolysis of the amine (IV; R = H, R′ = NH_2) to the hydroxy-compound failed under both acid and alkaline conditions.

When 2-nitroso-1-naphthylamine was condensed with cyanoacetamide, the isomeric 3-amino-5 : 6-benzoquinoxaline-2-carbonamide (IV; R = NH_2, R′ = CO·NH_2) was obtained.

(IV)   (V)

The amino-amides are valuable intermediates for the synthesis of a number of compounds in which a pyrimidine ring is fused to a pyrazine ring, as in pteridine and its derivatives (Gowenlock, Newbold, and Spring, *J.*, 1948, 517; Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 4219; Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1651; 1953, **75**, 1904), and this is the simplest unequivocal route to them. Prolonged heating of the aminobenzoquinoxalinecarbonamide (IV; R = CO·NH_2, R′ = NH_2) with ethyl chloroformate (Gowenlock, Newbold, and Spring, *loc. cit.*) gave an excellent yield of the urethane (IV; R = CO·NH_2, R′ = NH·CO_2Et), and this underwent ring closure in ethanol in the presence of sodium ethoxide to yield 6 : 8-dihydroxy-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = R′ = OH).

(*b*) Although 4-amino-2 : 6-dihydroxy-5-nitrosopyrimidine does not react with 2-naphthol to any noticeable extent, it is possible to produce the dihydroxytetra-azabenzanthracene (I; R = R′ = OH) by the inverse reaction, namely, the fusion of violuric acid with 2-naphthylamine.

Methylation by diazomethane of the dihydroxy-compounds obtained by both routes (*a* and *b*) yielded the *NN*′-dimethyldioxo-compound (II; R = R′ = Me), m. p. 278°, identical with the product obtained by the direct fusion method. Route (*a*), starting from a 1 : 2-disubstituted naphthalene, taken together with route (*b*) and the other typical fusion reactions involving a preformed pyrimidine ring, constitutes a complete structural proof of the series represented by (I) and (II).

With ethyl orthoformate and acetic anhydride (Albert, Brown, and Cheeseman, *J.*, 1951, 474), 2-amino-5 : 6-benzoquinoxaline-3-carbonamide (IV; R = CO·NH_2, R′ = NH_2) readily underwent ring closure to the monohydroxy-compound (I; R = OH, R′ = H) or its tautomer (V; R = H); if the period of reflux was shortened the intermediate 2-formamido-compound (IV; R = CO·NH_2, R′ = NH·CHO) was isolated, indicating the probable route by which 8-hydroxytetra-azabenzanthracene is formed. Treatment of the monohydroxy-compound with diazomethane yielded 7 : 8-dihydro-7-methyl-8-oxo-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (V; R = Me), the formulation of which as the *N*-methyl rather than the *O*-methyl compound is supported by the presence of a strong band at 1687 $cm.^{-1}$ corresponding to the vibration of a carbonyl group.

The monohydroxytetra-azabenzanthracene (I; R = OH, R′ = H) reacted with phosphorus pentasulphide in pyridine (Klingsberg and Papa, *J. Amer. Chem. Soc.*, 1951, **73**, 4988; Taylor, Carbon, and Hoff, *ibid.*, 1953, **75**, 1904) to yield the corresponding thiol (I; R = SH, R′ = H), which is of potential interest in view of the biological and clinical effects found with 6-mercaptopurine (Burchenal, Karnofsky, Murphy, Ellison, and Rhoads, *Proc. Amer. Assoc. Cancer Res.*, 1953, **1**, 7; Clarke, Philips, Sternberg, Stock, and Elion, *ibid.*, p. 9; Elion and Hitchings, *ibid.*, p. 13; Philips, Sternberg, Clarke, and Hitchings, *ibid.*, p. 42; Sugiura, *ibid.*, p. 55). An attempt was also made to pass from the monohydroxy-compound (I; R = OH, R′ = H) to the corresponding amino-compound but the necessary intermediate step of chlorination failed with phosphoryl chloride. However, the required monoamino-compound was prepared by the action of 4 : 6-diamino-5-nitrosopyrimidine on 2-naphthol, although in this case special conditions were required. If the two components were fused together in the manner described for triaminonitrosopyrimidine, a vigorous reaction occurred and the temperature rose spontaneously from 130° to 180° in a few seconds but the mixture, on being worked up at this stage, yielded only green amorphous material, suggesting that reaction was incomplete. More prolonged heating gave a little of the amino-compound (I; R = NH_2, R′ = H). The yield was improved by conducting the reaction in glacial acetic acid in the presence of sodium acetate and by careful purification.

When the fusion method was extended to 4-amino-6-hydroxy-5-nitrosopyrimidine in the hope of discovering a second, independent synthesis of the hydroxytetra-azabenzanthracene (I; R = OH, R′ = H), a vigorous reaction was again noted and, on one occasion, an impure specimen was isolated giving several spots on a paper chromatogram, one of the more weakly fluorescent of which corresponded with the required compound; on all other occasions, however, the product isolated was 2-amino-5 : 6-benzoquinoxaline-3-carbonamide (IV; R = CO·NH_2, R′ = NH_2). It seems probable that the fusion method yields the hydroxy-compound but that the correct conditions have yet to be discovered.

Reactions and Stability of Tetra-azabenzanthracenes.—Hydrolysis of the amino-groups of 6 : 8-diamino-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = R′ = NH_2) and its derivatives closely paralleled that of 2 : 4-diaminopteridines (Taylor and Cain, *J. Amer. Chem. Soc.*, 1949, **71**, 2538) in which use of strong acid replaces the 4-amino- by a hydroxy-group, while subsequent treatment with nitrous acid hydrolyses the 2-amino-group. A corresponding difference is shown by certain substituted aminopteridines, *e.g.*, leucopterin (Wieland, Metzger, Schöpf, and Bulow, *Annalen*, 1933, **507**, 226; Wieland and Purrmann, *ibid.*, 1940, **544**, 163), xanthopterin, and rhizopterin (Wolf, Anderson, Kaczka, Harris, Arth, Southwick, Mozingo, and Folkers, *J. Amer. Chem. Soc.*, 1947, **69**, 2753). Thus, (I; R = R′ = NH_2) with 6N-hydrochloric acid yielded an aminohydroxy-derivative, which with nitrous acid gave the dihydroxy-compound (I; R = R′ = OH), and thence with diazomethane the *NN*′-dimethyl compound (II; R = R′ = Me), thus linking the series (I) and (II) once more. That the intermediate aminohydroxy-compound was probably (I; R = OH, R′ = NH_2) was shown by hydrolysis of 8-amino-6-dimethylamino- (I; R = NH_2, R′ = NMe_2) to give 6-dimethylamino-8-hydroxy-tetra-azabenzanthracene (I; R = OH, R′ = NMe_2), this structure being confirmed synthetically by heating 4-amino-2-dimethylamino-6-hydroxy-5-nitrosopyrimidine with 2-naphthol (this reaction proceeds satisfactorily, in contrast to that with the diaminohydroxynitrosopyrimidine, presumably owing to the greater solubility of the dimethylamino-compound).

An attempt was made to use the preferential acid hydrolysis of the 8-amino-group to pass from 8-amino- (I; R = NH_2, R′ = H) to 8-hydroxy-tetra-azabenzanthracene, in order to provide corroborative evidence of the latter structure. However, the product was 2-amino-5 : 6-benzoquinoxaline-3-carboxylic acid (IV; R = CO_2H, R′ = NH_2). This result suggested that a tetra-azabenzanthracene bearing only an 8-substituent was less stable than those in which both available positions in the pyrimidine moiety were substituted and, in confirmation, it was shown that 8-hydroxytetra-azabenzanthracene was hydrolysed in a few minutes by hot N-sodium hydroxide to yield 2-amino-5 : 6-benzoquinoxaline-3-carbonamide (IV; R = CO·NH_2, R′ = NH_2). Contrariwise, the dihydroxytetra-azabenzanthracene (" benzalloxazine ") requires drastic hydrolysis to destroy the

pyrimidine ring (Wolf, Beutel, and Stevens, *loc. cit.*). This order of stability is similar to that found by Albert, Brown, and Cheeseman (*J.*, 1952, 4219) for the related pteridine compounds.

The instability of the 8-monosubstituted tetra-azabenzanthracenes explains the difficulties met in their preparation by fusion of the corresponding aminonitrosopyrimidines with 2-naphthol, since this reaction proceeds with the liberation of water at an elevated temperature.

Ultra-violet Absorption Spectra.—Throughout this work we have relied on both paper chromatography and ultra-violet absorption spectra to follow the purification of these somewhat intractable compounds. In general, absorption for the tetra-aza-1 : 2-benzanthracene is confined to two well-defined bands: one at 280—305 mμ (log ε 4·2—4·5), which may show fine structure to a degree depending on the nature of the substituents; and the other at 400—420 mμ (log ε 4·0—4·3), consisting of an inflexion and a maximum, which in one case becomes two well-defined maxima. Within these limits the spectra do not depend upon the number or nature of the substituents in the pyrimidine portion of the molecule (see Table). The spectra of *N*-methyl- and *NN'*-dimethyl-dioxotetra-azabenzanthracene closely resemble those of the diaminotetra-azabenzanthracenes. This is a little surprising since methylation of both nitrogen atoms in the one case has effectively blocked any tautomerism in the pyrimidine ring, which can no longer possess a typical aromatic structure except insofar as the dizwitterionic form (VI) can contribute to the resonance hybrid. This similarity in spectra between the diamino- and the dioxo-compound (II; R = R' = Me) must not be construed as evidence favouring a " di-imino "-structure for the former compound. In the related pteridine series the ultra-violet absorption spectra do not support " imino "-structures for the aminopteridines (Albert, Brown, and Cheeseman, *J.*, 1952, 1620, 4219) and evidence is accumulating against such forms in other heterocyclic systems (Clews and Cochran, *Acta Cryst.*, 1948, **1**, 4; 1949, **2**, 46; Broomhead, *ibid.*, 1948, **1**, 324; Angyal and Angyal, *J.*, 1952, 1461; Angyal and Werner, *ibid.*, p. 2911; Goulden, *ibid.*, p. 2939; Boarland and McOmie, *ibid.*, pp. 3716, 3722; Brown and Short, *J.*, 1953, 331). Marshall and Walker (*J.*, 1951, 1004; see also Boarland and McOmie, and Brown and Short, *locc. cit.*), working at controlled pH's—a desirable precaution which is largely precluded in our case by solubility requirements—concluded that the keto-form is favoured for hydroxypyrimidines and the same appears true of certain, at least, of the hydroxypteridines (Albert, Brown, and Cheeseman, *locc. cit.*). At the moment we wish merely to point out the possible importance of zwitterion forms such as (VI).

Ultra-violet absorption spectra of 5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracenes.*

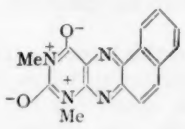
(Solvent: 4·5% formic acid, unless otherwise stated.)

	Absorption maxima					Absorption maxima			
	Band I		Band II			Band I		Band II	
Substituents	λ	log ε	λ	log ε	Substituents	λ	log ε	λ	log ε
8-Amino	290	4·32	409 *	4·11	8-Amino-6-dimethyl-	283	4·32	407	4·25
	300 †	4·26	417	4·13	amino	289	4·33	421	4·23
8-Hydroxy	292 *	4·34	392 †	3·97		302·5	4·26		
	299	4·37	403·5	4·01	6-Dimethylamino-8-	304	4·35	400 *	3·95
6 : 8-Diamino	281	4·26	405 *	4·17	hydroxy			411	4·00
	290	4·28	414	4·19	5 : 6 : 7 : 8-Tetrahydro-	291	4·03	397 *	3·87
	302	4·34			7-methyl-6 : 8-dioxo [2]	302	3·98	408·5	3·91
6-Amino-8-hydroxy [1]	291	4·58	395 †	4·27	5 : 6 : 7 : 8-Tetrahydro-	291	4·25	398 *	4·08
	300	4·57	407	4·32	5 : 7-dimethyl-6 : 8-	302	4·22	410	4·11
6 : 8-Dihydroxy	289	4·19	395 *	4·035	dioxo [2]				
	300	4·24	404	4·06					

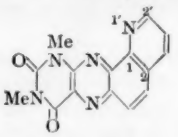
[1] Solvent: 36% formic acid. [2] Solvent: 22·5% formic acid.
* Inflexion. † Shoulder.

Related Compounds.—Some attempt has been made to extend the scope of the reaction between 4-amino-5-nitrosopyrimidines and 2-naphthol to include reaction with 1-naphthols. 1-Naphthol itself undoubtedly undergoes exothermic reaction with certain 4-amino-5-nitrosopyrimidines, *e.g.*, 2 : 4 : 6-triamino-5-nitrosopyrimidine, and crude yellow-brown products may be isolated, but these have so far resisted purification. 8-Hydroxyquinoline

may behave as a 1-naphthol in this sense and, although it does not react with the triaminonitrosopyrimidine, it combines with 4-amino-1 : 2 : 3 : 6-tetrahydro-1 : 3-dimethyl-5-nitroso-2 : 6-dioxopyrimidine to yield what is probably 5 : 6 : 7 : 8-tetrahydro-6 : 8-dimethyl-5 : 7-dioxo-1′ : 6 : 8 : 9 : 10-penta-aza-1 : 2-benzanthracene (VII). 6-Hydroxyquinoline reacts with triaminonitrosopyrimidine, but the product has not been purified.



(VI)



(VII)

Biological Results.—Through the kindness of Dr. H. O. J. Collier (Ware, Herts), a number of the substances described in this communication have been tested microbiologically as potential anti-folic or anti-folinic acid compounds. Only one, the diamino-compound (I; R = R′ = NH_2) which was weakly anti-folic, possessed significant activity.

Experimental

M.p.s were determined in electrically-heated copper blocks. Absorption spectra were measured by using a Unicam photoelectric spectrophotometer (Model SP 500). Fluorescence, both in solution and on paper chromatograms, was observed in ultra-violet light from a Hanovia lamp. All compounds were purified to constant ultra-violet absorption and/or single-spot purity on paper chromatograms on Whatman No. 1 filter paper. Analyses were by Mr. F. Oliver, Imperial College of Science and Technology, and Mr. P. R. W. Baker, Beckenham.

2-Amino-5 : 6-benzoquinoxaline-3-carbonamide (IV; R = $CO{\cdot}NH_2$, R′ = NH_2).—(*a*) 1-Nitroso-2-naphthylamine (0·86 g.), followed by cyanoacetamide (0·45 g.), was added to a solution from sodium (0·15 g.) in 2-ethoxyethanol (25 ml.), and the mixture refluxed for 5 min. while yellow crystals were precipitated. These (0·7 g.) were collected after chilling in ice and were recrystallised from 2-ethoxyethanol to yield the *carbonamide* as yellow needles, m. p. 282—283° (Found: C, 65·45; H, 4·3; N, 23·3. $C_{13}H_{10}ON_4$ requires C, 65·5; H, 4·2; N, 23·5%). The compound exhibits an intense light green fluorescence in glacial acetic acid solution and a greenish-blue fluorescence on a paper chromatogram. The *2-acetamido*-derivative, obtained by using hot acetic anhydride, formed yellow needles, m. p. 264—265°, from dimethylformamide (Found: C, 64·0; H, 4·6; N, 20·65. $C_{15}H_{12}O_2N_4$ requires C, 64·3; H, 4·3; N, 20·0%) and gave an intense green fluorescence in acetic acid.

(*b*) 2-Naphthol (4·0 g.) was fused at 130° and 4-amino-6-hydroxy-5-nitrosopyrimidine (0·63 g.; Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2593) was added in one portion. When the very vigorous reaction had subsided, the cooled melt was triturated with ether, and the insoluble material removed. The ethereal filtrate was partly evaporated and then deposited a yellow solid, which after crystallisation from glacial acetic acid and then 2-ethoxyethanol gave yellow needles, m. p. 282—283°, undepressed on admixture with a specimen prepared as in (*a*).

2-Amino-5 : 6-benzoquinoxaline-3-carboxylic acid (IV; R = CO_2H, R′ = NH_2).—(*a*) 1-Nitroso-2-naphthylamine (0·6 g.) and cyanoacetic acid (0·32 g.) were added to a solution of sodium (0·2 g.) in 2-ethoxyethanol (20 ml.), and the mixture boiled under reflux for 15 min. to yield a thick precipitate (0·46 g.) which was cooled and collected. The precipitate was boiled with N-hydrochloric acid (100 ml.) and then made strongly alkaline with aqueous ammonia (*d* 0·880) to yield a solution which was clarified with charcoal and filtered. Acidification of the filtrate gave a yellow crystalline precipitate which was recrystallised from glacial acetic acid, affording the *acid* as yellow needles, m. p. 232° (effervescence) (Found: C, 65·3, 65·1; H, 3·4, 3·7; N, 18·0, 17·7. $C_{13}H_9O_2N_3$ requires C, 65·3; H, 3·8; N, 17·6%).

(*b*) 1-Nitroso-2-naphthylamine (1·72 g.) and methyl cyanoacetate (1·1 g.) were refluxed for 1½ hr. with sodium (0·25 g.) in dry 2-ethoxyethanol (25 ml.). The yellow crystalline precipitate (0·7 g.) was collected, dissolved in hot water (charcoal), filtered, and acidified with dilute hydrochloric acid to give a solid, which recrystallised from glacial acetic acid as yellow needles, m. p. 229° (effervescence), undepressed on admixture with the product described in (*a*).

2-Amino-3-methoxycarbonyl-5 : 6-benzoquinoxaline (IV; R = CO_2Me, R′ = NH_2).—2-Amino-5 : 6-benzoquinoxaline-3-carboxylic acid (1 g.), suspended in acetone (10 ml.), was treated with diazomethane (from nitrosomethylurea, 4 g.) in ether (30 ml.), vigorous evolution of nitrogen occurring. After 24 hr., the precipitate (0·8 g.) was collected and crystallised from ethanol,

affording the *methyl* ester as yellow matted silky needles, m. p. 225—226° (Found: C, 66·4, 66·4; H, 4·9, 4·7; N, 16·6, 16·55. $C_{14}H_{11}O_2N_3$ requires C, 66·4; H, 4·4; N, 16·6%).

2-Amino-5 : 6-benzoquinoxaline (IV; R = H, R′ = NH_2).—The aminobenzoquinoxaline-3-carboxylic acid (1 g.) was heated at *ca.* 250°. When evolution of carbon dioxide ceased, the mass (0·6 g.) obtained after trituration with ether was crystallised from dilute ammoniacal dimethylformamide and yielded 2-amino-5 : 6-benzoquinoxaline as microscopic rods, m. p. 219—220° (Found: C, 73·5; H, 4·8; N, 21·65. Calc. for $C_{12}H_9N_3$: C, 73·8; H, 4·65; N, 21·5%) (Wolf, Beutel, and Stevens, *J. Amer. Chem. Soc.*, 1948, **70**, 2572, give m. p.s 150—152° and 215—217° for the 2- and the 3-amino-isomer). With hot 6N-hydrochloric acid it formed the *hydrochloride*, pale yellow silky needles, m. p. 277—278° (decomp.), from glacial acetic acid (Found: C, 62·5, 62·4; H, 5·0, 5·0. $C_{12}H_9N_3$,HCl requires C, 62·2; H, 4·35%). The amine exhibits a blue fluorescence in acid solution, which is unchanged on basification.

3-Amino-5 : 6-benzoquinoxaline-2-carbonamide (IV; R = NH_2, R′ = $CO{\cdot}NH_2$).—2-Nitroso-1-naphthylamine (1·72 g.) and cyanoacetamide (0·92 g.) were heated under reflux with a solution from sodium (0·2 g.) in ethanol (50 ml.). At the b. p. a thick precipitate of yellow needles was formed and after 1 min. the mixture was cooled and filtered. Crystallisation of the precipitate from 2-ethoxyethanol (charcoal) afforded the *carbonamide* as yellow needles, m. p. 255—256° (Found: C, 65·8; H, 4·3; N, 23·7. $C_{13}H_{10}ON_4$ requires C, 65·5; H, 4·2; N, 23·5%). The compound exhibits a bright green fluorescence in glacial acetic acid.

Tetra-aza-1 : 2-benzanthracenes.

8-Amino-6-dimethylamino-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = NH_2, R′ = NMe_2).—2-Naphthol (4 g.) was fused at 130° (internal temperature) and 4 : 6-diamino-2-dimethylamino-5-nitrosopyrimidine (1·8 g.; Roth, Smith, and Hultquist, *J. Amer. Chem. Soc.*, 1951, **73**, 2864) was added all at once with stirring. When the temperature of the melt was then slowly raised to 150° a vigorous reaction ensued, the temperature rising to 170—180°. When the reaction subsided, the melt was cooled and was extracted with ether. The yellow residue (2·24 g.), crystallised from 2-ethoxyethanol, afforded the *aminodimethylamino*-compound as clusters of orange blades with a pronounced bronze lustre, m. p. 340° (Found: C, 66·2, 66·3; H, 4·9, 4·75; N, 29·4, 29·4. $C_{16}H_{14}N_6$ requires C, 66·2; H, 4·8; N, 29·0%).

6-Dimethylamino-8-hydroxy-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = OH, R′ = NMe_2).—This was similarly prepared from 2-naphthol (6 g.) and 4-amino-2-dimethylamino-6-hydroxy-5-nitrosopyrimidine (1·83 g.; Roth *et al.*, *loc. cit.*) at 140—180°. The yellow-brown insoluble product (2·6 g.), obtained after extraction with ether, was crystallised from aqueous ethanol and gave the *tetra-aza-benzanthracene* as golden-yellow needles, m. p. 360° (Found: C, 61·6, 61·6; H, 5·2, 4·8; N, 22·7, 22·7. $C_{16}H_{13}ON_5$,H_2O requires C, 62·1; H, 4·9; N, 22·6. Found, in a sample dried at 150° in a high vacuum: C, 65·7, 65·7; H, 4·6, 4·6; N, 24·4, 24·5. $C_{16}H_{13}ON_5$ requires C, 66·0; H, 4·5; N, 24·0%).

8-Amino-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = NH_2, R′ = H).—A variety of experimental conditions were tried for the reaction of 2-naphthol with 4 : 6-diamino-5-nitrosopyrimidine, but chromatographic examination of the products after attempted purification demonstrated the existence of several contaminants. The following procedure was eventually adopted: 2-Naphthol (4·8 g.) and 4 : 6-diamino-5-nitrosopyrimidine (4·2 g.; Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2587) were dissolved in glacial acetic acid (30 ml.), and anhydrous sodium acetate (3 g.) was added. The mixture was refluxed for 1¼ hr., then diluted to 180 ml. with water. The precipitate obtained on addition of excess of concentrated aqueous ammonia was ground with concentrated hydrochloric acid (30 ml.) to form a hydrochloride, which was washed with methanol and then with ether. It was then suspended in water and made alkaline (Clayton-yellow paper) with dilute sodium hydroxide solution. The collected base was dissolved in hot 2% formic acid (charcoal) and again precipitated by the addition of dilute aqueous ammonia solution. After several crystallisations from butanol, the *amino*-compound formed yellow crystals, m. p. 343°, single-spot chromatographic purity (Found: C, 67·9; 67·9, H, 4·05, 3·9; N, 28·3, 28·0. $C_{14}H_9N_5$ requires C, 68·0; H, 3·7; N, 28·3%).

8-Hydroxy-5 : 7 : 9 : 10-tetra-aza-1 : 2-benzanthracene (I; R = OH, R′ = H).—(*a*) 2-Amino-5 : 6-benzoquinoxaline-3-carbonamide (1·2 g.; see above) was refluxed for 1 hr. with ethyl orthoformate (10 ml.) and acetic anhydride (10 ml.), and the cooled suspension (1·1 g.) was collected. The solid, crystallised from glacial acetic acid, yielded *2-formamido-5 : 6-benzoquinoxaline-3-carbonamide* as yellow needles, m. p. 398—400° (decomp.) (Found: C, 63·2; H, 4·0; N, 21·0. $C_{14}H_{10}O_2N_4$ requires C, 63·15; H, 3·8; N, 21·0%).

(*b*) The aminobenzoquinoxalinecarbonamide (6·0 g.) was refluxed with ethyl orthoformate (100 ml.) and acetic anhydride (100 ml.) for 4 hr. The precipitated crystals (5·1 g.) were collected and recrystallised from glacial acetic acid, giving the *hydroxytetra-aza-benzanthracene* as yellow needles, slowly decomposing above 340° (Found: C, 67·3, 67·65; H, 3·0, 3·2; N, 22·1, 22·0. $C_{14}H_8ON_4$ requires C, 67·7; H, 3·25; N, 22·5%). A solution of the substance in glacial acetic acid exhibited a pale yellow fluorescence.

7 : 8-*Dihydro*-7-*methyl*-8-*oxo*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (V; R = Me).—The hydroxy-tetra-aza-compound (1 g.), suspended in acetone (40 ml.), was treated with diazomethane (from nitrosomethylurea, 4 g.) in ether (40 ml.) and after 4 days at room temperature the *product* (0·75 g.) was collected and crystallised from butanol as irregular yellow prisms, m. p. 316—317° (Found: C, 68·8, 68·6; H, 3·7, 4·0; N, 21·5, 21·6. $C_{15}H_{10}ON_4$ requires C, 68·7; H, 3·8; N, 21·4%). Infra-red absorption in Nujol mull: strong band at 1687 cm.$^{-1}$.

8-*Mercapto*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = SH, R′ = H).—The hydroxy-tetra-aza-compound (1·25 g.), in dry pyridine (30 ml.), was treated with phosphorus pentasulphide (1·2 g.), and the mixture refluxed for 1½ hr. and then poured into hot water (100 ml.). The cooled suspension was collected and the solid (1·4 g.) crystallised several times from pyridine, to afford the *mercapto*-compound as beautiful bronze leaflets, m. p. 356° (decomp.) (Found: C, 62·9, 62·9; H, 3·55, 3·2; N, 21·6. $C_{14}H_8N_4S$ requires C, 63·6; H, 3·05; N, 21·2%). The compound gave a positive reaction with azide–iodine reagent, diagnostic for a mercapto-group (Feigl, "Qualitative Analysis by Spot Tests," Elsevier, New York, 1947, p. 353), and exhibited a pale blue fluorescence in water, which became white on addition of alkali. It did not yield a fluorescent spot on a paper chromatogram.

6 : 8-*Dihydroxy*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (I; R = R′ = OH).—(a) *From* 2-*aminobenzoquinoxaline*-3-*carbonamide*. A suspension of the amide (1 g.) in ethyl chloroformate (25 ml.) was refluxed for 40 hr., during which hydrogen chloride was slowly evolved. The ester was removed under reduced pressure and the residue (1·3 g.) crystallised from ethanol, to afford 2-*ethoxycarbonylamino*-5 : 6-*benzoquinoxaline*-3-*carbonamide* (IV; R = CO·NH$_2$, R′ = NH·CO$_2$Et) as sheaves of flat yellow prisms, m. p. >360° (Found: C, 62·05, 62·2; H, 4·7, 4·5; N, 18·1, 17·9. $C_{16}H_{14}O_3N_4$ requires C, 61·9; H, 4·55; N, 18·1%). The compound shows a bluish-white fluorescence in acetic acid. This urethane (0·5 g.) was added to a solution of sodium (0·5 g.) in dry ethanol (50 ml.), and the mixture refluxed for 3 hr., during which a precipitate separated. The solvent was evaporated under reduced pressure, the residue was dissolved in hot 2% sodium hydroxide solution, and the solution was filtered from a small amount of insoluble matter and acidified to yield a yellow precipitate (0·26 g.), m. p. >400°. This was identified by methylation by diazomethane (see below).

(b) *From violuric acid and* 2-*naphthylamine. The "inverse" fusion reaction.* 2-Naphthylamine (6 g.) was fused and violuric acid (1·6 g.) was added when the internal temperature was 130°. A vigorous reaction occurred when the temperature reached 150° and after a further ½ hr. at this temperature the melt was allowed to cool and was extracted successively with ethanol and warm 2N-sodium hydroxide. The filtered alkaline extract was acidified with dilute acetic acid, and the yellow precipitate was crystallised from 80% formic acid to yield the dihydroxy-compound as flat yellow needles, m. p. >400° (Found: C, 60·1, 60·0; H, 3·4, 3·6; N, 19·8, 19·9. $C_{14}H_8O_2N_4,1H_2O$ requires C, 59·6; H, 3·6; N, 19·85. Found, in a sample dried at 150° in a high vacuum: C, 63·6, 63·7; H, 3·2, 3·2; N, 21·1, 21·2. Calc. for $C_{14}H_8O_2N_4$: C, 63·6; H, 3·05; N, 21·2%). The compound gives a pure blue fluorescence both in solution and on paper chromatograms.

5 : 6 : 7 : 8-*Tetrahydro*-5 : 7-*dimethyl*-6 : 8-*dioxo*-5 : 7 : 9 : 10-*tetra-aza*-1 : 2-*benzanthracene* (II; R = R′ = Me).—(a) *By direct condensation.* 4-Amino-1 : 2 : 3 : 6-tetrahydro-1 : 3-dimethyl-5-nitroso-2 : 6-dioxopyrimidine (1·84 g.; Traube, *Ber.*, 1900, **33**, 3035) was added to fused 2-naphthol at 130° and, after the vigorous reaction had subsided, the melt was extracted with ethanol and ether to leave a yellow powder (1·82 g.). This was crystallised from 80% formic acid to give the *NN*′-dimethyl compound as pale yellow needles, m. p. 278° (Found: C, 66·2, 66·2; H, 4·1, 4·0; N, 19·1, 19·5. Calc. for $C_{16}H_{12}O_2N_4$: C, 65·8; H, 4·1; N, 19·2%). The compound gave a pure blue fluorescence in acetic acid solution and on paper. Kuhn and Cook (*loc. cit.*) give m. p. 258—260°.

(b) *By methylation of the dihydroxy-compound.* 6 : 8-Dihydroxy-5 : 7 : 9 : 10-tetra-aza-benzanthracene (0·5 g.; obtained by several routes) was suspended in acetone (20 ml.) and treated at room temperature with diazomethane (from nitrosomethylurea, 2 g.) in ether (20 ml.), and the precipitate (0·35 g.) collected after 2 or 3 days. Crystallisation from 80% formic acid gave pale yellow needles, m. p. and mixed m. p. 276—278°.

5 : 6 : 7 : 8-*Tetrahydro*-5-*methyl*-6 : 8-*dioxo*-5 : 7 : 9 : 10-*tetra*-*aza*-1 : 2-*benzanthracene* (II; R = H, R′ = Me).—The fusion reaction between 2-naphthol (4 g.) and 4-amino-3 : 6-dihydro-2-hydroxy-3-methyl-5-nitroso-6-oxopyrimidine (1·7 g., Traube, *loc. cit.*) was carried out at 150° for ½ hr. The residue (2·7 g.), isolated in the usual way, crystallised from a large volume of 80% formic acid to give the *monomethyl* derivative as pale yellow flat needles, m. p. 390° (Found: C, 64·6, 64·8; H, 3·7, 3·7; N, 20·6, 20·6. $C_{15}H_{10}O_2N_4$ requires C, 64·8; H, 3·6; N, 20·2%). This compound is very much less soluble than the related dimethyl compound. It too gives a pure blue fluorescence both in glacial acetic acid and on paper.

5 : 6 : 7 : 8-*Tetrahydro*-6 : 8-*dimethyl*-5 : 7-*dioxo*-6 : 8 : 9 : 10-*tetra*-*aza*-1 : 2-*benzanthracene* (III; R = R′ = Me).—(*a*) 1 : 2-Diaminonaphthalene hydrochloride and alloxan were condensed together, following Kühling's experimental conditions (*loc. cit.*, p. 2363), and the crude product purified by dissolving it in dilute sodium hydroxide solution (charcoal) and acidifying the filtrate with acetic acid. The precipitate (0·6 g.) was treated at room temperature with diazomethane (from nitrosomethyl-urea, 2 g.) in ether (20 ml.), and the product was collected after 2 days. It was dissolved in 50% acetic acid (150 ml.), and the insoluble residue crystallised from 80% acetic acid to yield the pure *NN′*-dimethyl compound as bright yellow needles, m. p. 318° (Found: C, 65·75, 65·9; H, 4·0, 4·3; N, 19·1, 19·3. Calc. for $C_{16}H_{12}O_2N_4$: C, 65·8; H, 4·1; N, 19·2%). This isomer exhibits a yellowish-green fluorescence in acetic acid, and a nearly pure green fluorescence on paper. The original mother-liquors (50% acetic acid) were cooled and filtered from deposited solid (m. p. 314°), and the filtrate was evaporated. The residue so obtained was crystallised twice from small volumes of 50% acetic acid: the product had m. p. 226°. Paper chromatography showed the presence of the isomer of m. p. 318° in large amounts (to judge from the intensity of fluorescence of the spot), but failed to yield a spot corresponding in position or colour of fluorescence with the isomer of m. p. 278°.

(*b*) 1 : 2-Naphthaquinone was condensed with 4 : 5-diamino-2 : 6-dihydroxypyrimidine, following Kuhn and Cook's directions (*loc. cit.*), and the crude product was purified by crystallisation from glacial acetic acid. Methylation of this compound with diazomethane, followed by crystallisation of the product from glacial acetic acid, afforded the isomer, m. p. and mixed m. p. 318°.

5 : 6 : 7 : 8-*Tetrahydro*-6 : 8-*dimethyl*-5 : 7-*dioxo*-1′ : 6 : 8 : 9 : 10-*penta*-*aza*-1 : 2-*benzanthracene* (VII).—4-Amino-1 : 2 : 3 : 6-tetrahydro-1 : 3-dimethyl-5-nitroso-2 : 6-dioxopyrimidine (1·84 g.) was added to fused 8-hydroxyquinoline (6 g.), and the melt was maintained at 180° for ½ hr. The cooled mass was thoroughly extracted with ethanol and ether, and the residue (1·06 g.) was repeatedly crystallised from a large volume of boiling water (charcoal), to yield the *penta*-*aza*-*benzanthracene* as yellow needles, m. p. 360° (Found: C, 60·5, 60·5; H, 3·6, 3·8; N, 23·3, 23·4. $C_{15}H_{11}O_2N_5,\frac{1}{4}H_2O$ requires C, 60·6; H, 3·9; N, 23·5%).

Alkaline Hydrolysis of 8-*Hydroxytetra*-*azabenzanthracene*.—The hydroxy-compound (0·25 g.) was boiled under reflux for 10 min. with N-sodium hydroxide (10 ml.), and the mixture was then allowed to cool and was filtered. The residue (0·125 g.) crystallised from 2-ethoxyethanol to form yellow needles, m. p. 278°, undepressed on admixture with 2-amino-5 : 6-benzoquinoxaline-3-carbonamide (m. p. 282°).

Acid Hydrolysis of 8-*Aminotetra*-*azabenzanthracene*.—The amino-compound (0·19 g.) was refluxed with 6N-hydrochloric acid (20 ml.) for 6 hr. and the suspension was collected after refrigeration. From glacial acetic acid it formed yellow crystals, m. p. 232°, undepressed on admixture with authentic 2-amino-5 : 6-benzoquinoxaline-3-carboxylic acid.

Acid Hydrolysis of 6 : 8-*Diaminotetra*-*azabenzanthracene*.—The diaminotetra-azabenzanthracene (0·7 g.; Felton and Timmis, *J.*, 1954, 2881) was refluxed with 6N-hydrochloric acid (60 ml.) for 9 hr. and the solid was then collected and extracted with 2N-sodium hydroxide. The filtered extract was acidified and gave 6-*amino*-8-*hydroxy*-5 : 7 : 9 : 10-*tetra*-*aza*-1 : 2-*benzanthracene*, which on crystallisation from 80% formic acid afforded lemon-yellow crystals, m. p. >400° (Found: C, 60·2; H, 3·95; N, 25·3. $C_{14}H_9ON_5,H_2O$ requires C, 59·8; H, 3·9; N, 24·95%). The compound exhibited an intense green fluorescence in acetic acid solution and a bluish-green fluorescence on paper.

Hydrolysis of 6-*Amino*-8-*hydroxytetra*-*azabenzanthracene by Nitrous Acid*.—The amino-hydroxy-compound (0·2 g.) was dissolved in concentrated sulphuric acid (7 ml.) and water (2 ml.), and the solution was cooled to −5° and decomposed by the addition of excess of solid sodium nitrite in small portions. After the pasty mass had been kept at room temperature for 15 min., it was heated on a steam-bath till effervescence ceased and then poured into ice water. The yellow solid precipitated was collected and crystallised from 80% formic acid, to yield yellow needles, m. p. >400°, which were identified as the dihydroxytetra-azabenzanthracene by comparison with an authentic specimen on a paper chromatogram and by treatment with

excess of diazomethane to give the tetrahydrodimethyldioxo-compound, m. p. and mixed m. p. 278°.

Acid Hydrolysis of 8-Amino-6-dimethylaminotetra-azabenzanthracene.—8-Amino-6-dimethylaminotetra-azabenzanthracene (1·15 g.) was refluxed with 6N-hydrochloric acid (80 ml.) for 7 hr. When cold, the solution was filtered and the insoluble residue (0·85 g.) was dissolved in hot dilute sodium hydroxide solution (charcoal), filtered, and acidified with dilute acetic acid. The yellow crystalline precipitate was recrystallised from aqueous ethanol and yielded the 6-dimethylamino-8-hydroxy-compound as golden-yellow needles, m. p. and mixed m. p. 357°.

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The Calculation of Formation Curves of Metal Complexes from pH *Titration Curves in Mixed Solvents.*

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The formation curve of a system of metal–ligand complexes can be calculated directly from pH-meter readings during a titration, without knowlege of the hydrogen-ion concentration or activity. Simple general equations, which can be used for all ligands which are conjugate bases to weak acids, are derived, and their application to specific systems illustrated. The method, which is valid both in water and in mixed solvents, gives stoicheiometric stability constants of the metal complexes. Stoicheiometric stability constants of the ligand–proton complexes can also be obtained. The possibility of converting stoicheiometric constants into thermodynamic constants is discussed.

CALVIN and WILSON (*J. Amer. Chem. Soc.*, 1945, **67**, 2003) have shown that pH measurements made during titration with alkali of a solution of a chelating agent, in the presence and in the absence of metal ions, could be used to calculate the free ligand exponent, pL, the degree of formation of the system, $\bar{n}$, and thence the stability constants, K_n, of the metal–ligand complexes present (J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941). Explicit equations have since been deduced at length by Maley and Mellor for acetylacetone, salicylaldehyde, 8-hydroxyquinoline and its 5-sulphonic acid, histidine, and glycine and its analogues (*Austral. J. Sci. Res.*, 1949, *A*, **2**, 92, 579). Albert has dealt with amino-acids with two or more ionising groups (*Biochem. J.*, 1950, **47**, 531; 1952, **50**, 690), Vickery with ethylenediaminetetra-acetic acid (*J.*, 1952, 1895), and other authors have treated, *e.g.*, diamines (J. Bjerrum, *Kgl. Danske Videnskab.*, 1945, **22**, 1773; Carlson, McReynolds, and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1334), polyamines (Jonassen, LeBlanc, Meibohm, and Rogan, *ibid.*, 1950, **72**, 4968; *J. Phys. Chem.*, 1952, **56**, 16), and complex polyamino-acids (Charabek and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 5052, 5057, 6021, 6228).

Owing to the variety of symbols employed, the equivalence of the different equations relating $\bar{n}$ and pL with experimentally determinable quantities is not immediately obvious. The following treatment is simpler, shorter, and quite generally applicable.

Charges being omitted for the sake of clarity, the stoicheiometric stability constant of the metal–ligand complex, ML_n, is defined by ${}^{C}K_n = [ML_n]/[ML_{n-1}][L]$, and that of the ligand–proton complex, LH_j, is defined by ${}^{C}K_j^{H} = [LH_j]/[LH_{j-1}][H]$. The overall stability constants are respectively defined as ${}^{C}\beta_n = {}^{C}K_1{}^{C}K_2{}^{C}K_3 \ldots {}^{C}K_n$ and ${}^{C}\beta_j^{H} = {}^{C}K_1^{H}.{}^{C}K_2^{H}. \ldots . {}^{C}K_j^{H}$.

Let the total concentration of ligand, metal, and dissociable hydrogen in the system be T_L, T_M, and T_H, respectively. Then for the degree of formation of metal–ligand complexes

$$\bar{n}_A = \frac{\text{total concentration of ligand bound to metal}}{\text{total concentration of metal}}$$

$$= \{T_L - (\text{concentration of ligand not bound to metal})\}/T_M \quad . \quad . \quad (1)$$

Similarily, for ligand–proton complexes,

$$\bar{n}_A = \frac{\text{total concentration of proton bound to ligand}}{\text{total concentration of ligand not bound to metal}}$$

$$= (T_H - [H])/(T_L - \bar{n}T_M) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Whence, from (1), $$\bar{n} = \{T_L - (T_H - [H])/\bar{n}_A\}/T_M \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

But $$\bar{n}_A = \sum_{j=1}^{j=J} j[LH_j] \Big/ \sum_{j=0}^{j=J} [LH_j] = \sum_{j=0}^{j=J} j\,{}^{C}\beta_j^{H}[H]^j \Big/ \sum_{j=0}^{j=J} {}^{C}\beta_j^{H}[H]^j \quad . \quad . \quad . \quad (4)$$

Finally, $T_L - \bar{n}T_M$ = concentration of ligand not bound to metal

$$= [L] \sum_{j=0}^{j=J} {}^{C}\beta_j^{H}[H]^j \text{ (where } \beta_0 = 1)$$

and $$pL = \log_{10}\left\{ \sum_{j=0}^{j=J} {}^{C}\beta_j^{H}[H]^j \Big/ (T_L - \bar{n}T_M) \right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Consider now the value of T_H in the general case. If to a concentration of mineral acid E is added sufficient ligand carrying dissociable hydrogen in the form H_yL to give a total ligand concentration T_L, then the total initial concentration of dissociable proton will be $E + yT_L$. Thus for ligands such as ammonia or ethylenediamine, $y = 0$; for glycine, oxine, acetylacetone, or salicylaldehyde, $y = 1$; for oxalic acid, or the disodium salt of ethylenediaminetetra-acetic acid, $y = 2$. Addition of alkali as sodium hydroxide, to give a sodium-ion concentration, Na (in excess of any due to neutral salt initially present), will reduce the total acidity to a value

$$T_H = E + yT_L - Na + [OH] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where the last term, usually negligible in comparison with the others, appears on account of hydrolysis.

Calculation of $\bar{n}_A$, $\bar{n}$, and pL from equations (2), (3), and (5) requires an accurate knowledge of [H], and two difficulties may arise. (i) If data are taken from a single pH titration curve for mineral acid and ligand, with or without metal present, then in the more acid solutions where Na and [OH] are negligible and where $E \gg T_L$, we have $[H] \sim E$. The calculated value of $T_H - [H]$ will then be very sensitive to small errors in [H]. The following procedure largely overcomes this difficulty. Fig. 1, curve 1, shows the titration curve for mineral acid alone, and curve 2 shows that for a mixture of mineral acid and ligand. Points on curve 1 are given by

$$[H]' = E' + [OH]' - Na' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

and from equation (2), points on curve 2 are given by

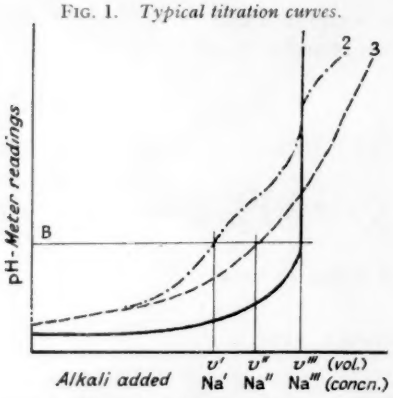
$$[H]'' = E'' + [OH]'' - Na'' + yT_L'' - \bar{n}_A''T_L'' \quad . \quad . \quad . \quad (8)$$

When pH-meter readings are identical for both solutions (ordinate B) $\{H\}' = \{H\}''$ and $\{OH\}' = \{OH\}''$, and if, further, the solutions have the same ionic strength, $[H]' = [H]''$, and $[OH]' = [OH]''$. It then follows that

$$\bar{n}_A'' = \{(E'' - E') - (Na'' - Na') + yT_L''\}/T_L'' \quad . \quad . \quad . \quad (9)$$

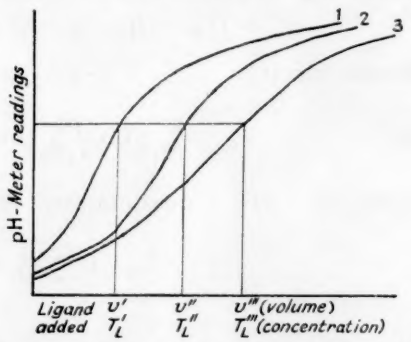
Suppose the initial volumes, V^0, the mineral acid concentrations, E^0, and the total ligand concentrations, T_L^0, were the same in each titration, and that volumes v', v'' of alkali, concentration N, were added to reach points Na', Na''.

FIG. 1. *Typical titration curves.*



Curve 1: *Mineral acid alone. Curve* 2: *mineral acid and ligand. Curve* 3: *mineral acid, ligand, and metal. Curves* 2 *and* 3 *are typical for ligands such as oxine. Although the relative disposition of the three curves depends on the nature of the ligands the argument in the text remains unchanged.*

FIG. 2. *Titrations with a solution of the ligand.*



Curves 1 *and* 2: *mineral acid at two different concentrations. Curve* 3: *mineral acid and metal ions.*

Then $E'' = V^0E^0/(V^0 + v'')$, $Na'' = v''N/(V^0 + v'')$, and $T_L'' = V^0T_L^0/(V^0 + v'')$. Similar equations can be obtained for E' and Na'. Then from (9),

$$\bar{n}_A = \left\{yT_L^0 + \frac{(v' - v'')(N + E^0)}{(V^0 + v')}\right\}\Big/T_L^0 \quad . \quad . \quad . \quad . \quad . \quad (10)$$

If, as in the work described in the following paper, $N \gg E^0$, and $V^0 \gg v'$, then,

$$\bar{n}_A = \left\{yT_L^0 + \frac{(v' - v'')N}{V^0}\right\}\Big/T_L^0 \quad . \quad . \quad . \quad . \quad . \quad (10a)$$

Values of $\bar{n}_A$ may thus be readily obtained from (10) or (10*a*). Although they are calculated from and correspond to particular pH-meter readings rather than to known hydrogen-ion concentrations or activities, such values of $\bar{n}_A$ may be used directly for calculating values of $\bar{n}$ for metal–complex formation as described later (p. 2907).

(ii) A second difficulty which arises is the calculation of values of the ligand–proton stability constants, K_j^H, from equation (4). To obtain j such constants, at least j widely separated values of $\bar{n}_A$ must be known (Irving and Rossotti, *J.*, 1953, 3397), but in every case the corresponding value of [H] is required. Now in aqueous solution we assume $-\log_{10}\{H\} = p\{H\} = B$, the reading of the pH-meter, since its readings have been correlated with known p{H} values of the buffer solutions used in "standardising" the instrument. Van Uitert and Haas (*J. Amer. Chem. Soc.*, 1953, **75**, 451) have recently shown that the more general relation

$$-\log_{10}[H] = B + \log f + \log U_H^0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

between hydrogen-ion concentration and pH-meter readings, B, is equally valid for water and for water–dioxan mixtures. Its use can be extended even to pure ethanol (van Uitert and Fernelius, *ibid.*, **1953**, **75**, 3862). Here f is the activity coefficient of hydrogen ions in the solvent mixture under consideration at the same temperature and ionic strength, and U_H^0 corresponds to the correction at zero ionic strength. For water, $U_H^0 = 1$, and at unit activity coefficient $[H] = 1/\text{antilog } B$. If then values of $1/\text{antilog } B = [H]f \,.\, U_H^0$ (in the general case) are substituted in equation (4) in place of the less easily determinable values of [H], there will result values for the proton–ligand stability constants which will be termed *practical constants*, denoted by ${}^pK_j^H$. These are related to the desired stoicheiometric constants by the expression

$$ {}^cK_j^H = fU_H^0 \, {}^pK_j^H \quad . . . . . \quad (11a) $$

further

$$ {}^c\beta_j^H = (fU_H^0)^j \, {}^p\beta_j^H \quad . . . . . \quad (11b) $$

$\log fU_H^0$ may be obtained as the intercept of the linear plot of p[H] against B, using solutions of known hydrogen-ion concentration, and used to convert *practical* constants into stoicheiometric constants. It will be shown later (p. 2908) that these refinements are not, in fact, necessary for calculating the stability constants of metal–ligand complexes.

Fig. 1, curve 3, shows a typical titration curve for a mixture of mineral acid, ligand, and metal ions. For any point on the curve,

$$ [H]''' = E''' + yT_L''' + OH''' - Na''' - \bar{n}_A'''T_L''' + \bar{n}_A'''\bar{n}'''T_M''' \quad (12) $$

If the pH-meter reading, B, and the ionic strength of this solution are the same as those given by equation (8) for a point on curve 2 (*i.e.*, the same ordinate, B), then $[H]'' = [H]'''$, $[OH]'' = [OH]'''$, and $\bar{n}_A'' = \bar{n}_A'''$, so that

$$ \bar{n} = \{(E'' - E''') + (T_L'' - T_L''')(y - \bar{n}_A) - (Na'' - Na''')\}/\bar{n}_A'''T_M''' \quad (13) $$

If the initial volumes, V^0, and concentrations of acid, E^0, and of ligand, T_L^0, were the same in each solution, and volumes v'' and v''' of alkali of concentration N were added to reach the points Na'' and Na''', then from (13)

$$ \bar{n}''' = (v''' - v'')\{N + E^0 + T_L^0(y - \bar{n}_A)\}/(V^0 + v'')\bar{n}_A'''T_M \quad . \quad (14) $$

Now if $N \gg E^0$, and $V^0 \gg v''$, then

$$ \bar{n}''' = (v''' - v'')N/V^0\,\bar{n}_A'''T_M \quad . . . . . \quad (14a) $$

Some computations illustrating the agreement between results obtained by using the approximate equations (10*a*) and (14*a*), and the rigorous equations (10) and (14) are shown in the accompanying table. It is seen that values of $\bar{n}_A$ and $\bar{n}$ obtained by using

B	4·00	4·00	5·25	6·25	9·50	11·00	11·50
$10^2v'$, ml.	1·667	1·667	1·683	1·683	1·693	1·707	1·721
$10^2v''$, ml.	1·197	1·197	1·450	1·643	1·721	1·898	2·100
$10^2v'''$, ml.	1·647	1·279	1·643	2·066	1·813	—	—
Metal ion	Cu^{++}	UO_2^{++}	Ni^{++}	Ni^{++}	Mg^{++}	—	—
$\bar{n}$ (i)	1·935	1·935	1·463	1·077	0·944	0·620	0·248
(ii)	1·921	1·921	1·456	1·076	0·943	0·625	0·262
Diff.....	0·014	0·014	0·007	0·001	0·001	0·005	0·014
$\bar{n}$ (i)	0·930	0·169	0·527	0·560	0·503	—	—
(ii)	0·918	0·167	0·520	1·538	0·496	—	—
Diff.....	0·012	0·002	0·007	0·022	0·007	—	—

Values in the rows preceded by (i) and (ii) are those calculated by equations (10), (14), and (10*a*), (14*a*) respectively; v''' refers to points on curves of the type 3 (Fig. 1) for the titration of 50% v/v aqueous dioxan containing 0·0200N-perchloric acid, 0·3M-sodium perchlorate, 0·006091M-8-hydroxy-2-methylquinoline, and 0·003045M-metal ions, with 1·175N-sodium hydroxide. In curve 2 (points v''), the metal is omitted, and in curve 1 (points v'), both metal and reagent are omitted. $V^0 = 9{\cdot}85$ ml. in each case, and $y = 1$.

the approximate equations seldom differ significantly from those obtained with the rigorous equations, unless the volume of alkali added is a considerable fraction of V^0.

Values of $\bar{n}_A$ appropriate to each pH-meter reading, B, have previously been obtained from equation (10), so that $\bar{n}$ can be calculated directly from pH-meter readings without any exact knowledge of the corresponding hydrogen-ion activities or concentrations. The calculation of pL from equation (5) would again appear to require a knowledge of [H], but, by a simple transformation,

$$\mathrm{pL} = \log_{10}\left\{\sum_{j=0}^{j=J} \frac{{}^{C}\beta_j^{H}}{(f\mathrm{U_H}^0)^j} \cdot ([\mathrm{H}]f{U_H}^0)^j \Big/ (T_L - \bar{n}T_M)\right\}$$

$$= \log_{10}\left\{\sum_{j=0}^{j=J} {}^{P}\beta_j^{H}(1/\mathrm{antilog}\ B)^j \Big/ (T_L - \bar{n}T_M)\right\} \quad . \quad . \quad . \quad . \quad (5a)$$

Hence equation (5) remains of the same form provided that (i) values of 1/antilog B are again used in place of [H], and (ii) the practical overall stability constants ${}^{P}\beta_j^{H}$, previously obtained for the ligand–proton complexes (cf. p.), are used in place of the stoicheiometric values ${}^{C}\beta_j^{H}$.

Having thus obtained corresponding values of $\bar{n}$ and pL, the formation curve of the metal–ligand system can be drawn, and values of ${}^{C}K_n$ calculated by the methods previously described (cf. Irving and Rossotti, *loc. cit.*, and references therein).

Titrations in which the Total Concentration of Ligand is varied.—In early studies of the stability of metal ammines, Bjerrum (*op. cit.*) obtained variations in pL by varying the total concentration of ligand in the system by discrete steps. Later workers (*e.g.*, Irving and Griffiths, *J.*, 1954, 213) carried out pH titrations with the amine as titrant. Here a solution containing metal ion and mineral acid is titrated with a solution of the ligand and, as in the method described above, $\bar{n}_A$ and $\bar{n}$ may be obtained directly from the horizontal displacement of titration curves.

In Fig. 2, curves 1 and 2 represent those in which solutions of mineral acid of initial concentration $E^{0\prime}$ and $E^{0\prime\prime}$ are titrated severally with a solution of ligand $\mathrm{H}_y\mathrm{L}$ of molar concentration L. When the ligand is added as the free base, *e.g.*, as ammonia or ethylenediamine, $y = 0$. Points on the two curves are given by

$$\text{Curve 1, } [\mathrm{H}]' = E' - [\mathrm{OH}]' - (\bar{n}_A' - y)T_L' \quad . \quad . \quad . \quad . \quad (15a)$$

$$\text{Curve 2, } [\mathrm{H}]'' = E'' - [\mathrm{OH}]'' - (\bar{n}_A'' - y)T_L'' \quad . \quad . \quad . \quad (15b)$$

Now for the same values of the ordinate B, if the solutions have the same ionic strength, $[\mathrm{H}]' = [\mathrm{H}]''$, and $[\mathrm{OH}]' = [\mathrm{OH}]''$, and

$$\bar{n}_A' = \bar{n}_A'' = (E'' - E')/(T_L'' - T_L') + y \quad . \quad . \quad . \quad . \quad (16)$$

If now the initial volume of both solutions was V^0, and if volumes v' and v'' of ligand solution were required to give the same pH-meter reading B on curves 1 and 2 respectively, then

$$\bar{n}_A = \frac{E^{0\prime\prime}(V^0 + v') - E^{0\prime}(V^0 + v'')}{L(v'' - v')} + y \quad . \quad . \quad . \quad . \quad . \quad (17)$$

and if $V^0 \gg v', v''$,

$$\bar{n}_A = y + (E^{0\prime\prime} - E^{0\prime})V^0/L(v'' - v') \quad . \quad . \quad . \quad . \quad . \quad (17a)$$

Fig. 2, curve 3, represents the titration curve of a volume V^0 of a solution containing metal ions and acid of initial concentrations T_M^0 and $E^{0\prime\prime}$, with a ligand solution of molar concentration L. For any point on curve 3,

$$[\mathrm{H}]''' = E'' + [\mathrm{OH}]''' - (\bar{n}_A''' - y)T_L''' + \bar{n}'''n_A'''T_M''' \quad . \quad . \quad . \quad (18)$$

If a volume v''' of ligand solution is required to give a pH-meter reading of B, then from (15*b*) and (18)

$$\bar{n}''' = (v''' - v'')\{E^{0''} + (\bar{n}_A'' - y)L\}/(V^0 + v'')\bar{n}_A'' T_M^0 \quad . \quad . \quad . \quad (19)$$

and if $V^0 \gg v''$, and $(\bar{n}_A'' - y)L \gg E^{0''}$, then

$$\bar{n}''' = (v''' - v'')(\bar{n}_A'' - y)L/V^0\bar{n}_A''T_M^0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (19a)$$

which reduces to

$$\bar{n}''' = (v''' - v'')L/V^0T_M^0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19b)$$

when the ligand is added as free base. Thus the use of equations (17) and (19) to give corresponding values of $\bar{n}_A$ and $\bar{n}$ for a series of pH-meter readings resembles that using equations (10) and (14) of p. 2907. In practice, however, it is often more convenient to obtained values of $\bar{n}_A$ from titrations of an acidic solution of the ligand with alkali [using equation (10)], and then to obtain values of $\bar{n}$ at the same pH-meter reading by the method just described using equation (19). All solutions must have the same ionic strength. In order to construct the formation curve, values of pL are calculated from equation (5*a*).

The Relationship between Values of ${}^{C}K_j^{H}$ *and Conventional Acid Dissociation Constants.*—The stability constants ${}^{C}K_j^{H}$ for ligand–proton complexes as defined above (p. 2904) are not,of course, identical with the conventionally defined classical dissociation constants of the various acids derived from L. It is customary to use the subscript 1 to designate the dissociation constant of the most acidic species, LH_J, so that

$${}^{C}K_1 = [H][LH]_{J-1}/[LH_J] = 1/{}^{C}K_j^{H}$$

For the next strongest acid

$${}^{C}K_2 = [H][LH_{J-2}]/[LH_{J-1}] = 1/{}^{C}K^{H}{}_{J-1}$$

For the dissociation of the final acid species, ${}^{C}K_J = [H][L]/[LH]$. In general, then, ${}^{C}K_j^{H} = 1/{}^{C}K_{J+1-j}$.

Thermodynamic Stability Constants.—The above procedures have given stoicheiometric stability constants which could be converted into thermodynamic constants were the appropriate activity coefficients available. For the uncharged complex, ML_2, of a univalent ligand and a bivalent cation, M^{++}, the second thermodynamic stability constant is given by ${}^{T}K_2 = \{ML_2\}/\{ML^+\}\{L^-\} = {}^{C}K_2 \cdot f_{ML_2}/f_{ML^+}f_{L^-} = {}^{C}K_2/f_{\pm}{}^2$ if it is assumed that the activity coefficient of the uncharged complex, ML_2, is unity, and independent of salt concentration, and that the product $f_{ML^+}f_{L^-}$ may be replaced by the square of the mean activity coefficient for hydrochloric acid in the same medium at the same ionic strength. Measurements by Van Uitert and Haas (*loc. cit.*) justify this assumption that the species ML^+ behaves as the cation of a strong electrolyte in aqueous dioxan, at least when M is a transition metal and HL is a 1 : 3-diketone. For the first stability constant

$${}^{T}K_1 = \{ML^+\}/\{M^{++}\}\{L^-\} = {}^{C}K_1 \cdot f_{ML^+}/f_{M^{++}}f_{L^-} = {}^{C}K_1/f^4$$

if we assume that the ratio f_{ML^+}/f_{L^-} is unity and unaffected by change of ionic strength, and that the activity coefficient $f_{M^{++}}$ for the doubly-charged ion equals the fourth power of the value for a singly-charged ion under the same conditions. Hence

$$\log {}^{T}K_1 = \log {}^{C}K_1 - 4 \log f_{\pm 1\text{-}1}$$

and, since measurements are made in the presence of a large concentration of neutral salt providing an excess of univalent anions, an equivalent expression can be shown to be

$$\log {}^{T}K_1 = \log {}^{C}K_1 + \log f^2_{\pm 1\text{-}1}/f^3_{\pm 2\text{-}1}$$

where the subscripts refer to 1–1- and 2–1-electrolytes respectively. In a basically similar treatment of thermodynamic stability constants Van Uitert and Haas (*loc. cit.*) deduce that

$$\log {}^{T}K_1 = -\log {}^{T}K_1{}^{H} + \log [ML^+]/[M^{++}] + \log [H^+]/[HL] + \log f^2_{\pm 1\text{-}1}/f_{\pm 2\text{-}1}$$

(in the nomenclature of the present paper) and note that the last term becomes zero and thus independent of ionic strength when the limiting case of the Debye–Hückel law can be applied. Of the two assumptions made in this derivation, *viz.*, (i) $f_{ML^+} = f_{H^+} = f_{L^-} = f_{\pm 1-1}$ and (ii) $f_{M^{++}} = f_{\pm 2-1}$, the latter is incorrect, and the last term of their equation should read $\log f^4_{\pm 1-1}/f^3_{\pm 2-1}$ and will be a function of ionic strength.

Similar calculations may be used to obtain thermodynamic stability constants for ligand–proton complexes and for metal–ligand complexes of different charge type. The assumptions can only be logically justified in dilute solutions, and, especially where ions of multiple charge are involved, it seems desirable always to report the values of stoicheiometric stability constants calculated from the experimental data together with the concentration and nature of the salt background used. Derived values of thermodynamic constants may then be corrected if and when more exact knowledge becomes available concerning the relevant activity coefficients.

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The Stabilities of Some Metal Complexes of 8-Hydroxyquinoline and Related Substances.

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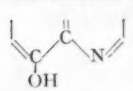
Dissociation constants of 8-hydroxyquinoline (and its 2-, 5-, 6-, and 7-methyl derivatives), 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine, 8-hydroxycinnoline (and its 4-methyl derivative), 8-hydroxyquinazoline (and its 2 : 4-dimethyl- and 4-methyl-2-phenyl derivatives), and 5-hydroxyquinoxaline, and the stability constants of the complexes they form with Mg^{++}, Zn^{++}, Ni^{++}, Cu^{++}, and UO_2^{++} ions have been measured in 50% v/v aqueous dioxan at 20°. Some factors affecting the stability of these complexes are discussed. Absorption spectra of 8-hydroxyquinazoline and 5-hydroxyquinoxaline and of their derivatives have been measured in acidic, neutral, and alkaline solution to provide further evidence for the position of the basic nitrogen atom in these compounds.

THE importance of 8-hydroxyquinoline ("oxine") and its derivatives in analytical chemistry (cf. Welcher, "Organic Analytical Reagents," van Nostrand, 1947, Vol. 1, Chap. XIII, XIV) has stimulated several quantitative studies of the stabilities of such reagents (*e.g.*, Maley and Mellor, *Austral. J. Sci. Res., A*, 1949, **2**, 92, 579; Albert, *Proc. Biochem. Soc.*, 1950, 47, xxvii; Näsänen *et al.*, *Acta Chem. Scand.*, 1951, **5**, 1199, 1293; 1952, **6**, 352, 837; 1953, **7**, 1261; *Suomen Kem.*, 1953, **32**, 11; Johnston and Freiser, *J. Amer. Chem. Soc.*, 1952, **74**, 5240). These measurements have been made under very different conditions of solvent composition and of ionic strength, and there is little coherent information on which to base a discussion of the effect of substituents in the oxine ring system on the stability of the corresponding metal complexes. The present work aims at a study of the variation in the stability of metal complexes with change in the environment of the functional group (inset). The chelating power of this group is modified by changing the inductive effects on the nitrogen atom and hydroxyl group, both by introducing substituents in the oxine skeleton, and by replacing one –CH= in the heterocyclic ring by –N=. Steric effects due to substituents near the functional group (*e.g.*, in the 2- and the 7-position in oxine) must also be considered.



Scope of the Work.—Stability constants, K_1 and K_2, where $K_n = [ML_n]/[ML_{n-1}][L]$, have been determined for the available reagents with the following bivalent ions selected for diversity of size and electronic configuration: Mg^{++}, Zn^{++}, Ni^{++}, Cu^{++}, and UO_2^{++}.

Measurements were made in 50% v/v aqueous dioxan, as many of the reagents and complexes are very sparingly soluble in water. A salt background of 0·3M-sodium perchlorate was used throughout, since in this mixed solvent the rate of change of activity coefficient with ionic strength is likely to be small at this concentration (Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950, p. 548).

Methods.—Stability constants of metal complexes were determined by the Calvin–Bjerrum pH-titration technique (Calvin and Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2003), and the dissociation constants of the reagents were determined by pH titration in the absence of metal ions. Typical titration curves obtained for oxine are shown in Fig. 1. Formation curves derived from these titrations appear in Fig. 2. The calculation of the dissociation constants and stability constants from the titration curves and the possibility of converting these values into thermodynamic constants is discussed in the preceding paper. All the values reported here are stoicheiometric concentration constants, valid only for the conditions of solvent and ionic background under which they were obtained.

The Dissociation Constants of the Reagents.—The stoicheiometric dissociation constants obtained at 20° in 50% v/v aqueous dioxan (0·3M-sodium perchlorate) are given in Table 1 together with the values of the dissociation constants in water, where these are known.

TABLE 1. *Dissociation constants of organic reagents at 20° in 50% v/v aqueous dioxan.*

		Aqueous solution			50% Aqueous dioxan		
No.	Reagent	pK_{OH}	pK_{NH}	Ref.	pK_{OH}	pK_{NH}	Ref.
1	8-Hydroxyquinoline	9·85	5·00	2	10·80	4·48	3
					11·54	3·97	4
2	8-Hydroxy-2-methylquinoline	10·31	5·54	5	11·01	5·01	3
					11·69	4·51	4
3	8-Hydroxy-5-methylquinoline	—	—	—	11·11	4·71	3
4	8-Hydroxy-6-methylquinoline	—	—	—	10·71	4·76	3
5	8-Hydroxy-7-methylquinoline	—	—	—	11·31	4·26	3
6	1 : 2 : 3 : 4-Tetrahydro-10-hydroxyacridine	—	—	—	11·39	5·49	3
7	8-Hydroxycinnoline	8·20	2·70	6	8·84	1·77	3
		8·13	2·86	7			
8	8-Hydroxy-4-methylcinnoline	8·67	3·28	7	9·00	2·59	3
9	8-Hydroxyquinazoline	8·65	3·41	6	9·59	3·30	3
		8·54	3·36	8			
10	8-Hydroxy-2 : 4-dimethylquinazoline	9·41	3·79	8	10·14	3·15	3
11	8-Hydroxy-4-methyl-2-phenylquinazoline	—	—	—	10·33	<1	3
12	5-Hydroxyquinoxaline	8·65	0·9	6	9·29	<1	3
		8·56	0·97	9			
		7·98	3·05	8			

(1) $pK_{OH} = \log [HA]/[H^+][A^-]$; $pK_{NH} = \log [H_2A^+]/[HA][H^+]$, where HA represents the neutral species. Thus $pK_{OH} = \log {}^{C}K_1^{H}$ and $pK_{NH} = \log {}^{C}K_2^{H}$ in the terminology of the preceding paper. Thermodynamic dissociation constants for the acids H_2A^+ and HA will be given by $\log {}^{T}K_1 = -pK_{NH}$ and $\log {}^{T}K_2 = -(pK_{OH} + 0{\cdot}74)$, $f_{\pm HCl}$ being taken as 0·43 by interpolation from data given by Harned and Owen (*op. cit.*). (2) Irving, Ewart, and Wilson, *J.*, 1949, 2672: thermodynamic constants obtained spectrophotometrically at room temperature. (3) Present authors: stoicheiometric constants obtained at 20° ± 0·2° and ionic strength 0·3M. (4) Johnston and Freiser (*loc. cit.*): Brønsted constants obtained at 25° by pH-titrations at unspecified ionic strength. (5) Phillips, *J. Amer. Chem. Soc.*, 1952, **74**, 552: Brønsted dissociation constants obtained spectrophotometrically at 25° ± 3° and ionic strength 0·1M. (6) Albert and Hampton, personal communication: Brønsted constants obtained by pH-titration at 20° and unspecified ionic strength. (7) Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009: thermodynamic constants obtained spectrophotometrically at 14° ± 3°. (8) Freeman and Spoerri, *J. Org. Chem.*, 1951, **16**, 438: no details given. (9) Irving and (Mrs.) Rossotti, unpublished work: thermodynamic constants obtained spectrophotometrically at 14° ± 3°.

It will be seen that pK_{OH} is increased by alkyl substitution in the 2-, 5-, and 7-positions of the oxine system, but is almost unchanged by a 6-methyl substituent. This is in accordance with the expected inductive effect. Methyl substitution also increases pK_{OH} in the aza-oxines studied. The observed lowering of pK_{OH} by aza-substitution has also been reported for some 4-hydroxyazaquinolines (Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356) and may be attributed to the electron-attracting power of the nitrogen atom.

As expected from the inductive effect, pK_{NH} is increased by alkyl substitution in the 2-, 5-, and 2 : 3-positions in oxine, the 4-position of 8-hydroxycinnoline (I), and the 2 : 4-positions

of 8-hydroxyquinazoline (II). The very low value of pK_{NH} of 8-hydroxy-4-methyl-2-phenylquinazoline may be attributed to blocking of the basic nitrogen atom by the large phenyl group (cf. Craig, *J.*, 1946, 534). The lowering of pK_{NH} in oxine by substitution of a methyl group in the 7-position may be due to a displacement of the hydroxyl group by the methyl group towards the basic nitrogen atom, thus hindering the approach of protons. The order of values of pK_{NH} for oxine and its aza-derivatives is the same as that established for the parent heterocyclics (Albert, Goldacre, and Phillips, *J.*, 1948, 2240) and, with the exception of 5-hydroxyquinoxaline (III), corresponds with that deduced from the calculations of relative charge distribution made by Longuet-Higgins and Coulson (*J.*, 1949, 971). The very low value obtained for 5-hydroxyquinoxaline differs widely from that reported by Freeman and Spoerri (*loc. cit.*) but is in good agreement with that of Albert and Hampton

FIG. 1. *The titration of 8-hydroxyquinoline and metal–oxine complexes in 50% v/v aqueous dioxan at 20°.*

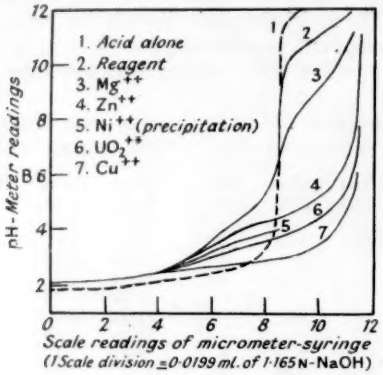
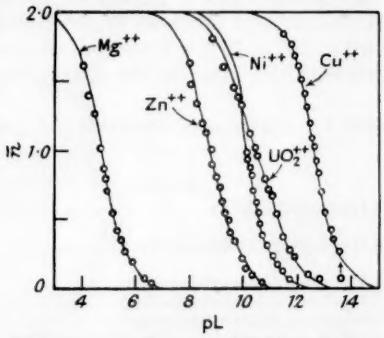
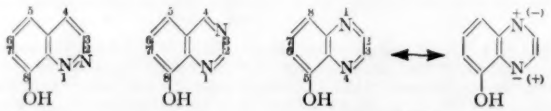


FIG. 2. *The formation curves of metal–oxine complexes in 50% v/v aqueous dioxan at 20°.*



Full curves are those calculated from values of K_1 and K_2 obtained from the experimental points (open circles).

(*loc. cit.*) and compatible with the very low value of pK_{NH} for the parent quinoxaline for which, following Albert, Goldacre, and Phillips (*loc. cit.*), we postulate very favourable resonance possibilities for the neutral molecule compared with those for the cation :



(I) (II) (III)

Such resonance would be less likely for cinnolines where the unlike charges would be less well separated. It would be impossible for quinazolines.

The increase in pK_{OH} observed on changing from water to a mixed solvent has frequently been noted for compounds in which a hydroxyl group dissociates (cf. Harned and Owen, *op. cit.*, p. 529; Van Uitert, Haas, Fernelius, and Douglas, *J. Amer. Chem. Soc.*, 1953, **75**, 455). The similar decrease in pK_{NH} has been reported for N–H dissociation in piperidine (Wynne-Jones and Salomon, *Trans. Faraday Soc.*, 1938, **34**, 1321) and in substituted anilines (James and Knox, *ibid.*, 1950, **46**, 1358). The increase in pK_{OH} and concomitant decrease in pK_{NH} with increasing organic content of a mixed solvent has previously been reported for oxine (Maley and Mellor, *loc. cit.*) but without comment, and it considerably complicates any quantitative prediction of the effect of solvent composition upon the stability of metal complexes derived from this type of reagent. An approach to a thermodynamic treatment of this problem will be discussed by the authors elsewhere.

The strengths of the –OH and $\gtrless\overset{+}{N}$–H bonds in the acids conjugate to oxine and its alkyl derivatives should be some index of the order of stability of the corresponding metal

complexes and, in the absence of steric and other complicating factors, a quantitative relationship between the stabilities of the metal–ligand and proton–ligand complexes might be expected (Calvin and Wilson, *loc. cit.*; Fernelius *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 457, 3862; Bruehlman and Verhoek, *ibid.*, 1948, **70**, 1401). Since $\Delta F_n = -2{\cdot}303\boldsymbol{R}T \log_{10} K_n$, the stability constants are really a measure of free-energy changes in the reaction and not simply of changes in the heats of bonding. The significance of entropy changes in complex formation has been discussed by Irving and Williams (*J.*, 1953, 3192).

The influence of pK_{NH} on complex formation in azaoxines is somewhat obscured by lack of conclusive evidence for the position of the more basic nitrogen (to which pK_{NH} refers) which might no longer be that one adjacent to the hydroxyl group.

The Position of the More Basic Nitrogen Atom.—Longuet-Higgins and Coulson's calculations (*loc. cit.*) indicate that, for the parent heterocyclic systems, the basic centre will be $N_{(1)}$ in both cinnoline and quinazoline, but in the latter the distribution of charge on the two nitrogen atoms is very similar and the position of the more basic centre might be changed by the presence of substituents. The parent quinoxaline is symmetrical. It has been found (Atkinson and Simpson, *J.*, 1947, 808; Simpson, *ibid.*, p. 1653) that $N_{(1)}$ is the basic centre in 4-methyl- and 4-amino-cinnoline. The large increase in pK_{NH} produced by the substitution of a methyl group in the 4-position of 8-hydroxycinnoline (Alford *et al.*, *loc. cit.*) also indicates that the more basic nitrogen atom is in the γ-position to the 4-substituent. In the quinazoline derivatives quaternary-salt formation takes place at $N_{(3)}$ in the parent (Gabriel and Colman, *Ber.*, 1904, **37**, 3643) and at $N_{(1)}$ in some 4-substituted derivatives (Morley and Simpson, *J.*, 1948, 360; 1949, 1354).

The absorption spectra of oxine, of 8-hydroxyquinazoline and its available derivatives, and of 5-hydroxyquinoxaline were studied in the hope of elucidating this problem. Measurements of optical absorption were made in alkali ($pH > pK_{OH} + 2$), in alcohol, and in acid ($pH < pK_{NH} - 2$) to give the spectra of the anion, neutral molecule, and cation respectively. The main features of the spectra, together with relevant data from the literature, are given in Table 2.

TABLE 2. *Absorption spectra.*

In 0·01N-HCl		In 95% MeOH		In 0·01N-NaOH		In 0·01N-HCl		In 95% MeOH		In 0·01N-NaOH	
λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
8-Hydroxyquinoline [1]						8-Hydroxyquinazoline					
252 *	4·76	243 *	4·54	252 *	4·49	242	3·67	242 *	4·39	255 *	4·42
270	2·47	275	3·13	290	2·91	258 *	3·83	265	2·83	285	2·92
310 *	3·21	310 *	3·40	335 *	3·45	280	3·48	325 *	3·41	338 *	3·56
315	3·20			345	3·44	298 *	3·72				
320 *	3·22			352 *	3·46	8-Hydroxy-2 : 4-dimethylquinazoline					
327	3·08					234	3·78	244 *	4·54	255 *	4·38
358 *	3·25					254 *	4·39	275	3·23	285	2·87
						280	3·23	330 *	3·51	335 *	3·59
8-Hydroxycinnoline [2]						300 *	3·41				
252 *	4·62	245 *	4·53	236 *	4·04	325	2·94				
290	3·00	269	2·63	240	3·95	365 *	3·17				
300 *	3·07	302 *	3·03	255 *	4·41	8-Hydroxy-4-methyl-2-phenylquinazoline [3]					
335	2·62	306	3·01	290	2·74	280 *	4·39	270 *	4·66	248	4·15
430 *	3·31	315 *	3·03	330 *	3·43	315	3·58	300	3·68	275 *	4·51
		320	3·01	356	2·94	335 *	3·67	330 *	3·76	310	3·29
		362 *	3·43	425 *	3·49					350 *	3·83
8-Hydroxy-4-methylcinnoline						5-Hydroxyquinoxaline [4]					
250 *	4·39	245 *	4·44	255 *	4·40	264 *	4·32	252 *	4·53	245	4·15
290	3·03	268	2·68	288	2·76	290	2·74	288	2·96	265 *	4·51
305 *	3·14	310 *	3·09	330 *	3·45	340 *	3·65	325 *	3·38	298	2·92
335	2·46	320	3·05	360	3·02	361	2·69			320 *	3·02
420 *	3·43	360 *	3·50	420 *	3·59	420 *	2·96			351	2·72
										415 *	3·21

* Indicates maximum, otherwise minimum.

[1] Cf. Ewing and Steck's diagram, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.

[2] Alford, Irving, Marsh, and Schofield, *loc. cit.*

[3] 0·2N-Hydrochloric acid used in place of 0·01N.

[4] 5N-Hydrochloric acid used in place of 0·01N.

The bathochromic shift and slight decrease in the intensity of the long wave-length band shown by the cations of 8-hydroxy- and 8-hydroxy-4-methyl-cinnoline relative to the spectra of the neutral molecule are very similar to those observed for oxine and may be taken as further indication that $N_{(1)}$ is the more basic centre in these compounds. Similar shifts occur in 8-hydroxy-2 : 4-dimethyl- and -4-methyl-2-phenyl-quinazoline, but the spectrum of the cation of the parent 8-hydroxyquinazoline shows a hypsochromic shift relative to the neutral molecule and a slight increase in intensity. These observations support the suggestion that the more basic centre is $N_{(1)}$ in some 4-substituted quinazolines, but is at $N_{(3)}$ in other quinazoline derivatives. In acidic solutions the absorption spectrum of 5-hydroxyquinoxaline is very similar to that of oxine, but the assignment of the basic centre to $N_{(1)}$ is necessarily tentative in the absence of further data. Thus in all the reagents studied except 8-hydroxyquinazoline, pK_{NH} may always be taken as referring to that nitrogen atom which takes part in the chelation process.

Stabilities of the Metal Complexes.—Concentration stability constants for the various metal complexes at 20° in 50% v/v aqueous dioxan (0·3M-sodium perchlorate) are given in Table 3.

TABLE 3. *Stability constants of metal complexes at 20° in 50% v/v aqueous dioxan.*[1]

	Mg^{++}	Zn^{++}	Ni^{++}	Cu^{++}	UO_2^{++}
8-Hydroxyquinoline					
log K_1	5·04 (6·38) [2]	9·34 (9·96)	10·43 (11·44)	13·03 (13·49)	11·25
log K_2	4·29 (5·43)	8·22 (8·90)	9·97 (9·94)	12·35 (12·73)	9·64
8-Hydroxy-2-methylquinoline					
log K_1	3·73	8·66 (10·10)	8·52 (9·50)	10·22 (13·00)	≃9·4
log K_2	3·13	8·10 (9·07)	7·96 (8·50)	9·32 (11·64)	≃8·0
8-Hydroxy-5-methylquinoline					
log K_1	5·21	9·46	*	13·55	11·25
log K_2	4·47	8·40	—	12·35	9·52
8-Hydroxy-6-methylquinoline					
log K_1	5·09	*	*	*	10·89
log K_2	4·31	—	—	—	9·26
8-Hydroxy-7-methylquinoline					
log K_1	4·64	9·31	*	*	11·28
log K_2	4·12	8·11	—	—	9·78
1 : 2 : 3 : 4-Tetrahydro-10-hydroxyacridine					
log K_1	3·98	8·80	*	11·78	10·10
log K_2	3·56	7·86	—	10·40	8·20

	Mg^{++}	Zn^{++}	Ni^{++}	Cu^{++}	UO_2^{++}
8-Hydroxycinnoline					
log K_1	3·02	6·93	8·25	9·48	8·68
log K_2	2·18	5·80	7·23	8·59	7·16
8-Hydroxy-4-methylcinnoline					
log K_1	3·66	7·22	~8·5	*	9·00
log K_2	2·58	6·47	~8·2	—	7·30
8-Hydroxyquinazoline					
log K_1	3·89	7·48	*	10·56	8·99
log K_2	2·91	6·96	—	9·54	7·70
8-Hydroxy-2 : 4-dimethylquinazoline					
log K_1	3·81	7·77	7·88	10·26	8·77
log K_2	3·09	7·01	7·00	9·74	7·33
8-Hydroxy-4-methyl-2-phenylquinazoline					
log K_1	0	7·03	*	8·83	8·53
log K_2	—	5·87	—	8·31	7·85
5-Hydroxyquinoxaline					
log K_1	3·44	7·07	7·79	9·66	8·40
log K_2	2·95	5·71	7·02	8·84	7·51

* = Insoluble.

[1] The values quoted are concentration constants valid for a 0·3M-sodium perchlorate salt background. $f_{\pm HCl}$ being taken as 0·43 (interpolation from data by Harned and Owen, *op. cit.*), thermodynamic stability constants can be calculated from log $^TK_1$ = log $^CK_1$ + 1·48, and log $^TK_2$ = log $^CK_2$ + 0·74.

[2] Values in parentheses are those reported by Johnston and Freiser (*loc. cit.*), obtained by pH-titration at 25°. Although there is a systematic variation between the two sets of stability constants obtained for oxine complexes, there is little agreement between Johnston and Freiser's values and those we now report for 8-hydroxy-2-methylquinoline complexes.

The relation between the dissociation constant of a reagent and the stability of its metal complexes has been considered by Calvin and Wilson (*loc. cit.*), Fernelius *et al.* (*loc. cit.*), and Bruehlman and Verhoek (*loc. cit.*) but no quantitative treatment has been proposed. For a given metal and a series of reagents of similar type it can be shown * that the free energy of formation of the metal–ligand complex should be a linear function of the free energy of formation of the proton–ligand complex; the plot of log K_1 against pK for the reagent

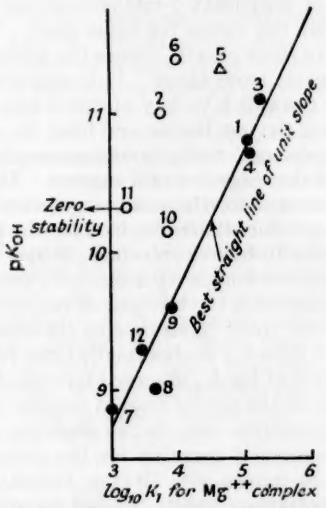
* A full discussion of the thermodynamic derivation of this and related equations will be published shortly (Irving and Rossotti, in preparation).

should be a straight line of unit slope. The plot for magnesium complexes is shown in Fig. 3 together with the best straight line of unit slope.

There are two types of deviation from the theoretically predicted behaviour. (*a*) Major deviations, where log K_1 is always smaller than predicted. These are invariably associated with reagents having substituents adjacent to the chelating nitrogen atom, and the stabilities of the metal complexes are clearly decreased by steric hindrance (cf. Irving, Butler, and Ring, *J.*, 1949, 1489). There is no evidence of complex formation between magnesium ions and 8-hydroxy-4-methyl-2-phenylquinazoline.

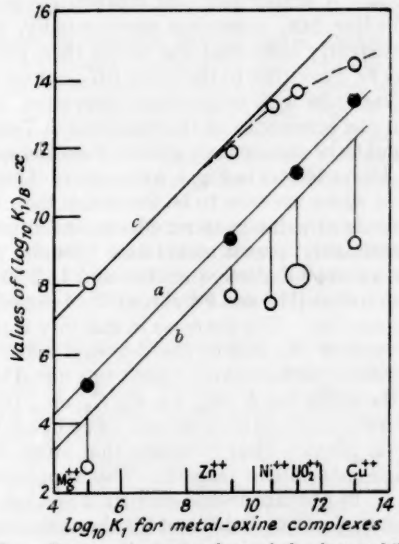
(*b*) Minor deviations, in which log K_1 may be either smaller or greater than predicted. Since both oxygen and nitrogen atoms are involved in complex formation, the magnitude

FIG. 3.



Open circles refer to reagents with substituents adjacent to the chelating nitrogen atom. The open triangle refers to the reagent with a substituent adjacent to the chelating oxygen atom. The numbers of the reagents are those given in Table 1.

FIG. 4. *Intercomparisons of the stability of metal complexes analogous to those of 8-hydroxyquinoline.*



The ordinates represent values of the first stability constants of metal chelates of (a) *8-hydroxy-5-methylquinoline*; $x = 0$. (b) *8-Hydroxy-2-methylquinoline*; $x = -1{\cdot}0$. (c) *8-Hydroxycinnoline*; $x = +5{\cdot}0$. *The straight lines have the theoretical slopes and intercepts* (*see text*).

of pK_{OH} is not the only factor which influences log K_1. The observed minor deviations may well be due to differences in the co-ordinating powers of the nitrogen atoms in the various reagents for which pK_{NH} forms a measure.

Data for zinc, nickel, and uranyl complexes when plotted in the same way resemble Fig. 3 in displaying large negative deviations for sterically hindered metal complexes; but the minor deviations are more marked than in the case of magnesium and it seems probable that the value of pK_{NH} for the reagent has a greater influence on the stability of complexes formed by these ions, which may form fairly strong metal–nitrogen bonds, than on those of magnesium, which forms only weak links to nitrogen. Indeed, if the metal ion is very strongly bonded to one of the chelating atoms it may appreciably modify the inductive effects on the other, so that any simple theoretical prediction of stability based upon the values obtained for the unchelated hydrogen complexes, *i.e.*, upon pK_{OH} and pK_{NH} may be unjustified. Such an effect would be most noticeable among copper complexes where, in fact, a small increase in pK_{OH} gives rise to an abnormally large increase in the

stability of the metal complex, and the slope of the best straight line in a plot of log K_1 against pK(reagent) is 2·2.

Any tendencies towards "specific" behaviour in reagents may be disclosed by comparing the stabilities of complexes formed by a series of cations with different pairs of ligands, A and B. If, for a given cation, the stability of the complex depended only on the strength of the corresponding ligand–hydrogen bond, then the plot of $(\log K_1)_A$ against $(\log K_1)_B$ for a series of cations should give a straight line of unit slope and of intercept $pK_A - pK_B$.* Some plots of this type, together with the theoretically predicted lines, are shown in Fig. 4, *a*, *b*, *c*, where the abscissæ represent values for log K_1 for oxine complexes in every case.

In Fig. 4, *a*, where values of log K_1 for 8-hydroxy-5-methylquinoline complexes are plotted as the ordinates, the experimental points fall closely on the theoretical line, as might be expected for reagents which differ only slightly in structure and in their values of pK_{NH}. A similar plot (not reproduced) is obtained for complexes of 8-hydroxy-6-methylquinoline but, somewhat unexpectedly, complexes of 8-hydroxy-7-methylquinoline are consistently somewhat less stable than predictable from the values for oxine itself. This may be due either to the lower pK_{NH} of the reagent or to steric effects. Since the deviation occurs even with magnesium complexes, the latter seems more likely. It is noteworthy that the sensitivity of the reactions of 7-methyloxine towards a variety of metal ions was found to be significantly greater than those of oxine itself (Irving, Butler, and Ring, *loc. cit.*).

The ordinates in Fig. 4, *b* are values of log K_1 for 8-hydroxy-2-methylquinoline complexes, all of which are seen to be less stable than the pK_{OH} of the reagent would suggest. This is undoubtedly due to steric effects, and it is especially marked for the small magnesium and (presumably) planar nickel ions. Similar plots (not reproduced) are obtained for the pairs of reagents 8-hydroxyquinoline and 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine; 8-hydroxyquinazoline (II), and 8-hydroxy-2 : 4-dimethylquinazoline or 8-hydroxy-4-methyl-2-phenylquinazoline. The decrease in stability is most noticeable with the last pair of reagents on account of the size of the 2-phenyl substituent. While steric hindrance to chelation of successive molecules of reagent to a metal ion should be reflected in abnormally large values of the ratios log K_1/K_2, log K_2/K_3, etc., the lower values of log K_1 observed for complexes of every 2-substituted reagent as compared with those for the parent reagent and the same metal provide clear evidence that steric factors are operative even in the chelation of a single molecule of reagent. This supplements results recently reported for the chelation of 1 : 10-phenanthroline and its 3-methyl derivative to ferrous iron (Irving, Cabell, and Mellor, *J.*, 1953, 3417) and for the chelation of ethylenediamine and its *N*-alkyl derivatives to various transition metals (Irving and Griffiths, *J.*, 1954, 213).

Values of log K_1 for complexes of 8-hydroxycinnoline form the ordinates in Fig. 4, *c*. The stability constant of the magnesium complex lies on the theoretical line, that for the copper complex lies well below it. Points for other cations are in intermediate positions. The low value of pK_{NH} for 8-hydroxycinnoline compared with the value for oxine would be expected to reduce the stability of its copper complex but to have little effect on that with magnesium. Similar plots (not reproduced) are obtained if values of log K_1 for 8-hydroxyquinazoline, 5-hydroxyquinoxaline, or 8-hydroxy-4-methylcinnoline are used as ordinates. If values of log K_1 for these reagents are plotted severally against those for 8-hydroxycinnoline, the experimental points lie much nearer to the theoretical line than when 8-hydroxyquinoline complexes are made the basis of comparison as in Fig. 3. Doubtless this is because the variation in pK_{NH} among these reagents is smaller.

The differences log K_1 − log K_2 for the various metal complexes studied do not indicate a purely statistical addition of the second ligand (Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941, p. 40). The differences observed show no definite trend, and it seems probable that the cation is so modified by the addition of the first ligand—not least so far as its solvation sheath is concerned—that the forces leading to the interaction of the singly charged 1 : 1 complex with a further molecule of ligand are of quite a different type and order from those operating between the solvated bivalent ion and the first molecule of ligand (cf. Fernelius *et al.*, *J. Amer. Chem. Soc.*, 1953,

* See footnote, p. 2914.

75, 2739, 3862). In none of the complexes investigated is $K_2 > K_1$. The values of K_1/K_2 are consistently high for all uranyl complexes.

Irrespective of the nature of the ligand the stability of these metal complexes always follows the order $Mg^{++} < Zn^{++} < Ni^{++} < UO_2^{++} < Cu^{++}$ whether steric hindrance occurs or not. The only exception is 2-methyloxine where the nickel complex is slightly weaker than the zinc complex. The extent of steric hindrance to complex formation (as estimated by deviations from the theoretical straight lines of Fig. 4) cannot be simply related to any properties of the ions or ligands investigated. Thus the order of increasing deviation is $Zn^{++} < Mg^{++} < UO_2^{++} < Cu^{++}$ for 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine, $Zn^{++} < Mg^{++} < Ni^{++} \cong UO_2^{++} < Cu^{++}$ for 2-methyloxine, but $Mg^{++} < Zn^{++} < Ni^{++} \cong UO_2^{++} < Cu^{++}$ for 8-hydroxy-2 : 4-dimethylquinazoline, and $Zn^{++} < UO_2^{++} < Cu^{++} < Ni^{++}$ for 8-hydroxy-4-methyl-2-phenylquinazoline.

Experimental

Materials.—Solutions of metal ions were prepared by weighing out " AnalaR " sulphates (or " AnalaR " uranyl nitrate) into " AnalaR " perchloric acid standardised against carbonate-free sodium hydroxide. Pure anhydrous sodium perchlorate was obtained from a good commercial specimen by repeated recrystallisation from water (Fronaeus, Diss., Lund, 1948, p. 21). " AnalaR " dioxan was used without further treatment and all water was redistilled from an all-Pyrex still. Carbonate-free sodium hydroxide was prepared as described by Vogel (" Quantitative Inorganic Analysis," Longmans, Green and Co., London, 1951, p. 234) and standardised against " AnalaR " potassium hydrogen phthalate, dried at 115°.

Pure oxine was available and the methyl-substituted oxines and the specimen of 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine had been previously prepared in this laboratory (Irving, Butler, and Ring, *loc. cit.*). We are indebted to Dr. K. Schofield, of University College, Exeter, for the cinnoline and quinazoline derivatives, and to Prof. A. Albert, of the Australian National University, for the gift of 5-hydroxyquinoxaline.

Apparatus.—Titrations were carried out at 20·0° ± 0·2° in a double-walled Pyrex-glass cell of total capacity 25 ml. Water from a thermostat circulated through the outer jacket. Alkali was added from an " Agla " micrometer syringe (capacity 0·5 ml.) fitted with a capillary glass nozzle bent at right angles to the barrel. The barrel was mounted horizontally and the micrometer screw advanced mechanically by a motor and reduction gear which gave 8 rev./min., equivalent to 0·08 ml./min. The syringe was calibrated by weighing, using mercury, and one large division was found to represent 0·01992 ± 0·00014 ml. The contents of the titration vessel were stirred by a stream of nitrogen freed from carbon dioxide and pre-saturated with solvent. A Doran " Alkacid " sealed glass electrode and a Pye dip-type microcalomel electrode with a fibre liquid junction were used. The pH-meter readings were measured to 0·01 unit with a Cambridge bench-type pH-meter, standardised before, and checked after, each titration with buffer solutions of pH 4·01 and 9·20 at 20° prepared from " Soloid " tablets (Messrs. Burroughs and Wellcome, Ltd.).

Titration Procedure.—The carbonate-free alkali was about 1·1N for all titrations. Solutions for the titration of metal complexes were prepared by pipetting 5·00 ml. of 0·0394N-perchloric acid containing 0·6M-sodium perchlorate and 0·006M-metallic salt into the titration vessel and adding 5·00 ml. of dioxan containing 0·012M-reagent. Titration of the reagent alone was carried out by using similar solutions but omitting the metallic salt, and titrations of the acid alone by omitting both metal and reagent. In some systems titrations were also carried out with half the metal concentration prescribed above, but the stability constants thence obtained did not differ by more than 0·02 unit from those determined at the higher metal concentration.

The change in volume on mixing water and dioxan was determined by measuring the densities of the pure liquids and of the mixture. The final volume was found to be 9·850 ± 0·004 ml. instead of 10·000. The concentrations of the reactants were calculated with allowance for this contraction and also for volume changes due to the addition of alkali during the titration (see preceding paper).

Calculations.—The method used for computing the formation curves for the various metal complexes (Bjerrum, *op. cit.*) from titration measurements has been described and discussed in the preceding paper. Thence stability constants were obtained by the " correction term " method (Irving and Rossotti, *J.*, 1952, 3397).

Spectrophotometric Measurements.—Absorption spectra were measured with a Beckman D.U.

Spectrophotometer using minimum slit widths and matched 1 cm. silica cells. Spectra of cations were obtained by using 5N-hydrochloric acid with 5-hydroxyquinoxaline, 0·2N for 8-hydroxy-4-methyl-2-phenylquinazoline, and 0·01N-hydrochloric acid for all other reagents. Spectra of the neutral molecules were measured in " 95% " methanol prepared by adding 5 ml. of distilled water to 95 ml. of redistilled methyl alcohol previously tested for its optical transparency. The spectra of the anions were obtained in 0·01N-sodium hydroxide. Concentrations of the reagents were varied from 10^{-3}M to 10^{-5}M depending upon the part of the spectrum under investigation. All reagents were shown to obey Beer's law in the three solvents in this concentration range.

Grateful acknowledgment is made to Imperial Chemical Industries Limited for the loan of a Beckman spectrophotometer, and to Dr. K. Schofield (University College, Exeter) and Professor A. Albert (Australian National University) for the gift of aza-oxines. One of us (H. S. R.) gratefully acknowledges a Grant from the Ministry of Supply.

INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, March 1st,* 1954.]

Mechanism of Substitution at a Saturated Carbon Atom. Part XXXIX. Nucleophilic Substitutions in Tertiary Alkyl Halides by Hydroxylic Reagents in Nitromethane Solvent.*

By EDWARD GELLES, E. D. HUGHES, and C. K. INGOLD.

[Reprint Order No. 5297.]

The reactions of *tert.*-butyl bromide with water, ethyl alcohol, and phenol, each alone, and in mixtures, in solvent nitromethane, with pyridine to limit the acidity, have the kinetic characteristics of unimolecular processes, involving a slow formation, and fast subsequent reactions, of the carbonium ion. With larger concentrations of substituting agents the rates rise linearly, and without mutual effects when mixtures of reagents are used. This is attributed to the electrophilic catalysis of ionisation, since the effect follows the acidity order, PhOH > HOH > EtOH. With still larger concentrations of water, a further acceleration sets in, which is ascribed to a macroscopic solvent effect.

The reactions of triphenylmethyl chloride with pyridine and the same reagents in nitromethane have kinetics which point to a mechanism derived from the same two stages with a reversed rate order, though now pyridine forms complexes with the carbonium ion. With increasing reagent concentrations, the rates rise linearly and without mutual terms, but now in the nucleophilic order, EtOH > HOH > PhOH, as would be expected if attack upon a preformed cation is rate-controlling, since then the reagents can only function as nucelophiles.

A summary is given of the possible modes of action of hydroxylic reagents on alkyl halides in solvolysis, and in non-solvolytic substitutions in polar and non-polar solvents. Kinetic consequences are indicated. Reference is made to the work of C. G. Swain in solvent benzene.

SUBSEQUENTLY to our earlier work on nucleophilic substitution in hydroxylic solvents, we took up the study of non-solvolytic substitution in aprotic polar solvents. A number of such reactions in solvent sulphur dioxide have already been described (*J.*, 1940, 1011, 1017; *J.*, 1954, 634, 642, 647). Our first reports on substitutions in nitromethane as solvent are now presented.

Interest in the mechanism of unimolecular reactions has led us to begin work in nitromethane (as we began it in sulphur dioxide) by examining reactions of some alkyl halides which have a known tendency to use that mechanism. We now report on certain reactions of *tert.*-butyl bromide and of triphenylmethyl chloride.

This paper relates specifically to the use, as nucleophilic substituting agents for these

* Part XXXVIII, *J.*, 1954, 647.

alkyl halides, of hydroxylic substances, the examples being water, ethyl alcohol, and phenol. Their special interest is that, had they been used as solvents, they would have effected solvolytic substitution. By investigating such non-solvolytic substitutions in nitromethane, we hoped to cast on the mechanism of solvolytic substitution a light which might not be unduly indirect for the following reason.

It is likely that, although no aprotic solvent can in general rival the best hydroxylic solvents in capacity for electrostatic solvation, nitromethane, owing to its large dipole moment and small molecular volume, comes nearer to doing so than do most other non-hydroxylic solvents. Thus nitromethane seemed to be a solvent in which we might study the specific actions of hydroxylic substituting agents, introduced as solutes, with relatively little interference from an assumption by such reagents of those non-specific functions of electrostatic solvation which we wanted still to belong to the solvent. The hope that specific actions by the hydroxylic compounds would stand sufficiently isolated to be elucidated, directed that our first use of nitromethane as solvent for nucleophilic substitution should be turned to this particular account.

(1) *Reactions of* tert.-*Butyl Bromide.*—The reactions studied were those of the alkyl halide with pyridine, and with water, ethyl alcohol, and phenol, separately and as mixtures, without or with added pyridine, and in some cases with an added salt. Experiments with comparable concentrations of the reactants enabled the kinetic order with respect to each to be established. Experiments were also made over a range of much higher concentrations of the hydroxyl compounds.

The chemical changes, as confirmed by analysis or isolation of the products, consisted of simultaneous elimination and substitution :

$$\mathrm{Bu^tBr + ROH} \begin{cases} \rightarrow \mathrm{Me_2C{:}CH_2 + HBr + ROH} \\ \rightarrow \mathrm{Bu^tOR + HBr} \end{cases}$$

where ROH stands for HOH, EtOH, or PhOH. The reactions were kinetically followed usually by the developed acid, but also sometimes by the formed bromide ion, the two methods giving identical results. With pyridine as reagent, and in the absence of hydroxy-compounds, the sole reaction is elimination, which with excess of pyridine goes to completion. In the absence of pyridine the reactions with the hydroxyl compounds come to equilibrium after only a small amount of change. But in the presence of a small excess of pyridine they run to completion, the acid and bromide ion appearing as pyridinium bromide. The main reaction is now one of substitution (including *C*-substitution in the case of phenol). The rates of all the reactions were independent of the pyridine concentration, as is illustrated for hydrolysis in Table 1.

TABLE 1. *First-order rate constants* (k_1 *in sec.*$^{-1}$) *of reaction of* tert.-*butyl bromide with water* (*or with water and ethyl alcohol*) *in nitromethane at* 25·0° : *illustrating invariance of rate with changing pyridine concentration.*

(Initially, [$\mathrm{Bu^tBr}$] ~ 0·07M.)

Run no.	7	10	5	6	11	28	26
$[H_2O]_0$	0·61	0·61	1·00	1·00	1·00	1·11	1·11
$[EtOH]_0$	—	—	—	—	—	0·33	0·33
$[Pyridine]_0$	0·00	0·075	0·00	0·075	0·11	0·00	0·075
10^5k_1	1·07	1·06	1·64	1·67	1·67	2·16	2·21

The initial specific rates of destruction of *tert.*-butyl bromide by all the reagents were independent of the initial concentration of the alkyl halide over the investigated range of 0·02—0·07M, as is illustrated for hydrolysis in Table 2. The overall reactions are thus of the first order with respect to the alkyl halide. In all the experiments cited later in this section the initial concentration of alkyl halide was kept within this range, whilst the concentration of added pyridine was standardised at 0·075M.

Except in special circumstances which will be noted, all individual runs were well

represented by the first-order rate law. This was true, not only for runs, such as those entered in Tables 1 and 2, in which the substituting agent was in large and nearly constant

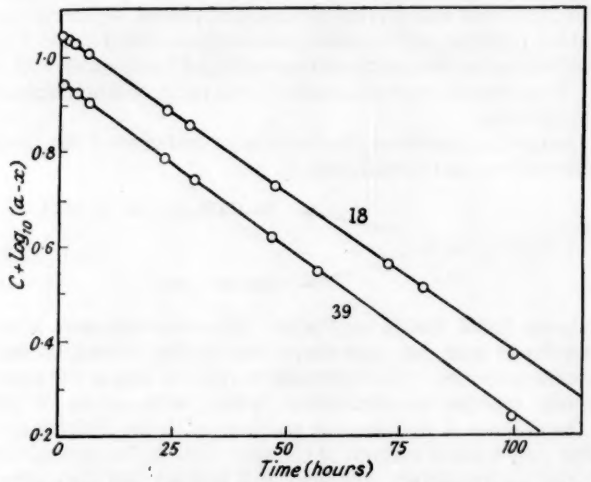
TABLE 2. *Initial specific rates (k_1 in sec.$^{-1}$) of reaction of* tert.*-butyl bromide with water in nitromethane at 25·0°: illustrating invariance of the specific rate with changing concentration of the alkyl halide.*

(Initially, $[H_2O] = 1{\cdot}00$M; [pyridine] from 0·00 to 0·11M.)

Run no.	16	15	14	11
$[Bu^tBr]_0$	0·0212	0·0350	0·0456	0·0691
10^5k_1	1·69	1·70	1·70	1·67

excess, but also for experiments in which the reagent was in concentration comparable to that of the alkyl halide. This is illustrated in Fig. 1 by plots, covering the first 80% of each of two runs, of the logarithm of the concentration of surviving alkyl halide *versus* the

FIG. 1. *Kinetic course of reactions of* tert.*-butyl bromide in nitromethane at 25·0°.*



Run 18: Initially, $[Bu^tBr] = 0{\cdot}069$M, [pyridine] = 0·075M, $[H_2O] = 0{\cdot}035$M.
Run 39: Initially, $[Bu^tBr] = 0{\cdot}069$M, [pyridine] = 0·075M, [EtOH] = 0·107M.

time. In one run the substituting agent is water present in moderate deficit, and in the other it is ethyl alcohol in moderate excess. Taking into account our knowledge, derived from isolation of products, that the actual amount of substitution in these conditions, as in all those we examined, approaches the stoicheiometric maximum, we have to conclude from linear plots such as those illustrated, not only that all reactions are of first order in the alkyl halide, but also that the substitutions are of zeroth order in the substituting agents.

The small deviations shown by the last points in Fig. 1 probably arise from a positive salt effect, which can, indeed, be brought out much more strongly by adding a salt, such as tetraethylammonium bromide, the rate then increasing from the outset, as is illustrated for alcoholysis in Fig. 2. Though we did not develop the study of salt effects quantitatively, the rate changes are certainly large enough to be understood as ionic-strength effects in unimolecular substitution. The relative retardations shown by the last few points in the most saline of the runs illustrated in Fig. 2, probably represent a small mass-law effect in the unimolecular mechanism, since it is here, if anywhere, that one would expect to find such retardations, namely, when the concentration of bromide ion is high, and nearly all the substituting agent has been used up, so that an appreciable proportion of formed carbonium ions fails to be collected by the substituting agent before it reunites with bromide ion.

When the concentration of hydroxylic substituting agent is made much larger than that of the alkyl bromide, say 10—50 times larger, then the first-order rate constant rises substantially, *e.g.*, by 2—7 times. This is illustrated in Table 3, for the reagents water, ethyl alcohol, and phenol, employed separately, and for the three possible types of binary mixtures of them.

The functional forms of the relations between rate and the concentrations of the three reagents, when used separately, are shown in Fig. 3. At low reagent concentrations, the main part of the rate is independent of the reagent: that is why we observe first-order rate-laws in these conditions. At high concentrations, the reagents are in constant excess, and we inevitably find first-order laws. Only in a few intermediate cases, indicated by the asterisks in Table 3, do we observe a slight falling-off in the first-order constants, suggesting

TABLE 3. *First-order rate-constants (k_1 in sec.$^{-1}$) of reactions of* tert.*-butyl bromide in nitromethane at 25·0°: variation with concentration of the substituting agent.*

(Initially, [Bu^{t}Br] = 0·02—0·07M, [pyridine] = 0·075M.)

Substituting agent: H_2O

Run no.	13, 17	18	45	42	38	10	44	11, 14—16	29, 30
$[H_2O]_0$	0·00	0·035	0·075	0·133	0·435	0·61	0·70	1·00	1·10
10^5k_1	0·395	0·43	0·47 *	0·53	0·84	1·06	1·195	1·69	1·90

Substituting agent: EtOH.

Run no.	13, 17	39	21	20	37	22	43
$[EtOH]_0$	0·000	0·107	0·330	0·67	1·00	1·33	1·59
10^5k_1	0·395	0·455	0·565	0·74	0·905	1·06	1·18

Substituting agent: PhOH.

Run no.	13, 17	55	56	57
$[PhOH]_0$	0·000	0·063	0·160	0·318
10^5k_1	0·395	0·525 *	0·825	1·26

Substituting agent: H_2O + EtOH.

Run no.	40	38	41	24	23	26	25	34	27
$[H_2O]_0$	0·10	0·11	0·22	0·50	1·00	1·10	1·10	1·10	1·10
$[EtOH]_0$	0·23	0·23	1·00	1·00	1·00	0·33	0·67	1·00	1·33
10^5k_1	0·615	0·615	0·135	1·59	2·56	2·21	2·48	2·63	2·88
Calc.	0·625	0·63	1·13	1·42	2·20	2·07	2·24	2·41	2·56

Substituting agent: H_2O + PhOH

Run no.	51	62
$[H_2O]_0$	0·10	0·10
$[PhOH]_0$	0·16	0·32
10^5k_1	0·925	1·37
Calc.	0·94	1·37

Substituting agent: EtOH + PhOH

Run no.	65	66
$[EtOH]_0$	0·33	0·67
$[PhOH]_0$	0·32	0·16
10^5k_1	1·40	1·18
Calc.	1·43	1·18

* Initial value: k_1 drops by a few units % as reaction proceeds.

that the reaction has an appreciable dependence on the reagent, and is being affected by the fall in its concentration with time.

As Fig. 3 shows, the rates increase linearly with the reagent concentration, except that, in the case of water, this simple relation holds only up to 0·5M, after which a steeper increase sets in. The linear rates at 25° are represented by the equations

$$\left.\begin{aligned} 10^5k_1^{HOH} &= 0{\cdot}40 + 1{\cdot}02\,[H_2O] \\ 10^5k_1^{EtOH} &= 0{\cdot}40 + 0{\cdot}50\,[EtOH] \\ 10_5k_1^{PhOH} &= 0{\cdot}40 + 2{\cdot}75\,[PhOH] \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In the lower three sections of Table 3, rows of figures headed "Calc." are given, which represent rates for binary mixtures of substituting agents, as calculated from the formula

$$k_1 = k_1^{ROH} + k_1^{R'OH} - 0{\cdot}40 \times 10^{-5} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where ROH, R'OH = HOH, EtOH, PhOH. The agreement is good, provided that water, if present, is in concentration below 0·5M. This must mean that, for the concentration

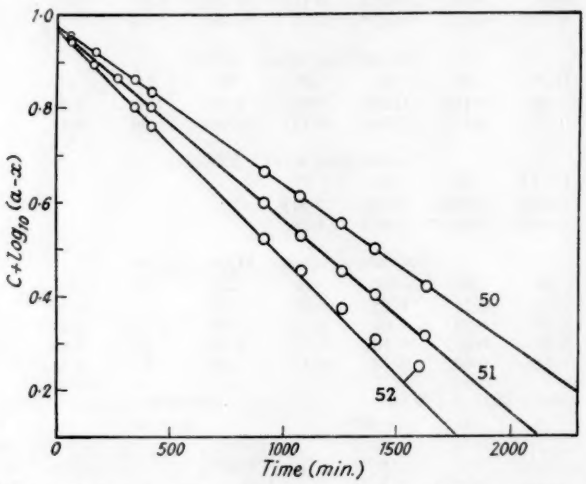
ranges over which the separate reagents affect the rate linearly, the rate for any mixture of them is given by an additive expression without " mutual " terms :

$$10^5 k_1 = 0{\cdot}40 + 1{\cdot}02\,[H_2O] + 0{\cdot}50\,[EtOH] + 2{\cdot}75\,[PhOH] \quad . \quad . \quad . \quad . \quad (3)$$

When the mixture of substituting agents contains water in concentrations from 0·5M upward, so that, if the water were there as the only substituting agent, it would produce rates in excess of the appropriate linear rates, then the observed rates for the mixed reagents are always higher than those calculated from equation (2), even though k_1^{HOH}, as used in this equation, is now taken from the experimental rate curve for water, and thus allows for the extra rate of the water reaction when water is in high concentration. It thus appears that water, when in concentration above 0·5M, has the power, not only of sharpening its influence on the rate of its own reaction, but also of accelerating the reaction of an independent substituting agent.

A brief study has been made of the temperature effect on rate, and of its analysis in terms of the Arrhenius equation, for the reaction with water in a concentration within the

FIG. 2. *Salt effects in reactions of* tert.*-butyl bromide in nitromethane at* 40·0°.



(All runs have, initially, [Bu^{t}Br] = 0·035M, [pyridine] = 0·075M, [EtOH] = 0·039M, whilst [NEt$_4$Br] is 0·000M in run 50, 0·045M in run 51, and 0·110M in run 52.)

range of its linear kinetic effect. The results are summarised in Table 4. These data are compared in the following paper with corresponding figures for some other substitution reactions of *tert.*-butyl bromide in nitromethane.

TABLE 4. *Arrhenius parameters of the rates of reaction of* tert.*-butyl bromide in nitromethane with water* (B_1 *in sec.*$^{-1}$, E *in kcal./mole*).

(Initially, [Bu^{t}Br] ~ 0·05M, [pyridine] = 0·075M.)

Run no.	[H_2O]	T	$10^5 k_1$	$\log_{10} B_1$	E
70	0·125	273·1°	0·0206		
42, 45	,,	298·1	0·519	9·76	20·6
76	,,	313·1	2·70		

Products of the elimination, and of the three substitutions, at 25° and at 40°, were separated and identified by standard methods from completed reactions, conducted in conditions similar to those of typical kinetic experiments, except that the scale, and in some cases the concentrations, were somewhat larger. Liquids, isolated by distillation through an efficient column of small hold-up, were identified by b. p. and refractive index. The

following example will illustrate the dominance of substitution in the presence of an equivalent or more of substituting agent. From *tert.*-butyl bromide (2·3 g.) and pyridine and water in equivalence (~0·3M) at 40° in nitromethane, 0·95 g. of *tert.*-butyl alcohol, b. p. 82·8°, n_D 1·388, was isolated: this yield is 75% of the theoretical.

(2) *Reactions of Triphenylmethyl Chloride.*—When this substance is dissolved in nitromethane, the characteristic greenish-yellow colour of the carbonium ion appears to be produced instantly. Bentley, Evans, and Halpern have shown (*Trans. Faraday Soc.*, 1951, **47**, 711) that this colour arises from the conversion of a small proportion of the solute molecules into ion-pairs, $Ph_3CCl \rightleftharpoons \{Ph_3C^+\}Cl^-$, the proportion of ion-pairs formed at 0°, for instance, being 0·032%, independently of concentration.

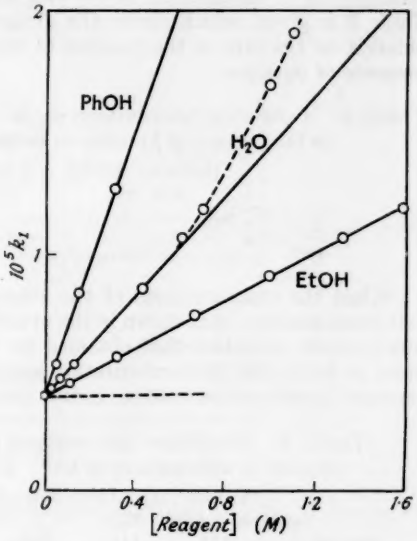


FIG. 3. *First-order rate-constants for reactions of* tert.*-butyl bromide in nitromethane at 25·0°, as functions of the concentrations of the substituting agents.*

When pyridine is added to such solutions, the colour is discharged instantly. No acid (*i.e.*, pyridinium ion) is developed.

When water, ethyl alcohol, or phenol is added to a solution of triphenylmethyl chloride in nitromethane, substitutions occur (including *C*-substitution in the case of phenol),

$$Ph_3CCl + ROH \rightleftharpoons Ph_3C{\cdot}OR + HCl$$

as can be followed by the development of acid. However, these reactions reach equilibrium after only a small percentage conversion. Thus, with initial concentrations $[Ph_3CCl] =$ 0·0211M, and $[EtOH] =$ 0·0248M, the concentration of acid developed at equilibrium is 0·0033M, corresponding to a 16% conversion.

On addition of water, ethyl alcohol, or phenol, or mixtures of them, to a solution of triphenylmethyl chloride and an excess of pyridine in nitromethane, the above substitutions proceed to completion. The reactions in these conditions have been followed kinetically at 0°, by noting the development of acid. Their rates are of the order of 100—1000 times greater than those of the corresponding reactions of *tert.*-butyl bromide.

Early in our kinetic investigation it was established, for the three substitutions with single substituting agents, that the rates are independent of the concentration of previously introduced pyridine, and that the specific rates are independent of the initial concentration of triphenylmethyl chloride. Individual runs followed first-order rate-laws to a good approximation, not only when the concentration of substituting agent was relatively high and therefore almost constant, but also when it was low, and, in particular, when, for water or phenol, it was comparable to the concentration of the triphenylmethyl chloride.

Thus reactions were occurring which are of first order in the alkyl halide and of zeroth order in the substituting agent. However, a range of intermediate reagent-concentrations could be found, easily in the case of ethyl alcohol, with some difficulty in that of water, and hardly at all in that of phenol, for which the first-order rate-constants fall off with the progress of reaction, thus indicating the presence of a component process which depends on the concentration of the substituting agent. All these results are so similar to those already described for the reactions of *tert.*-butyl bromide that separate illustration is omitted.

In contrast to the reactions of *tert.*-butyl bromide, those of triphenylmethyl chloride showed no salt effects, a clear indication that, despite a general similarity, the detailed mechanisms of substitution of the two alkyl halides are not the same. In illustration, Table 5 is given, which shows the absence of an effect of added tetraethylammonium chloride on the rate of the reaction of triphenylmethyl chloride with ethyl alcohol in the presence of pyridine.

TABLE 5. *First-order rate-constants (k_1 in sec.$^{-1}$) of triphenylmethyl chloride with ethyl alcohol in the presence of pyridine in nitromethane at 0·0° : absence of a salt effect.*

(Initially, [EtOH] = 0·0232M, [pyridine] = 0·062M.)

Run no.	103	104	105
$[Ph_3CCl]_0$	0·0197	0·0210	0·0197
$[NEt_4Cl]_0$	None	0·0795	0·1590
10^5k_1	13·1	12·8	13·1

When the concentrations of the substituting agents are considerably increased, the rate constants rise, as is shown in the upper sections of Table 6. Up to a point, this result qualitatively resembles that obtained for the reactions of *tert.*-butyl bromide; but the order in which the three substituting agents then stood, with respect to the sensitivity of the rate to their concentration, is now found to be inverted.

TABLE 6. *First-order rate-constants (k_1 in sec.$^{-1}$) of reactions of triphenylmethyl chloride in nitromethane at 0·0° : dependence on concentration of the reagent.*

(Initially, $[Ph_3CCl]$ = 0·02—0·05M, [pyridine] = 0·05—0·07M.)

Substituting agent : H_2O.

Run no.	113	114	115
$[H_2O]_0$	0·043	0·097	0·209
10^5k_1	9·5 *	15·8	32·0

Substituting agent : PhOH

Run no.	116	117	118
$[PhOH]_0$	0·044	0·173	0·255
10^5k_1	5·3	7·7	8·8

Substituting agent : EtOH.

Run no.	103	106, 107	108	110	111	112
$[EtOH]_0$	0·023	0·025	0·052	0·062	0·125	0·255
10^5k_1	13·1 *	17·5 *	28·1	34·3	68	140

Reagent : H_2O + EtOH.

Run no.	121
$[H_2O]_0$	0·097
$[EtOH]_0$	0·103
10^5k_1	69
Calc.	68

Reagent : H_2O + PhOH.

Run no.	122
$[H_2O]_0$	0·097
$[PhOH]_0$	0·044
10^5k_1	17·7
Calc.	17·1

Reagent : EtOH + PhOH.

Run no.	120	119
$[EtOH]_0$	0·025	0·048
$[PhOH]_0$	0·025	0·044
10^5k_1	16·0 *	28·0
Calc.	17·0	29·1

* From initial part of run : the constants fall as reaction continues.

Within the ranges of concentration investigated (up to 0·25M), the increases of reaction-rate with increasing reagent concentration were substantially linear, as illustrated in Fig. 4. For the three substituting agents, separately employed, the first-order rate-constants at 0° are given approximately by the following equations :

$$\left.\begin{aligned} 10^5k_1^{HOH} &= 4{\cdot}0 + 125\,[H_2O] \\ 10^5k_1^{EtOH} &= 4{\cdot}0 + 500\,[EtOH] \\ 10^5k_1^{PhOH} &= 4{\cdot}0 + 25\,[PhOH] \end{aligned}\right\} \quad \cdots\cdots\cdots \quad (4)$$

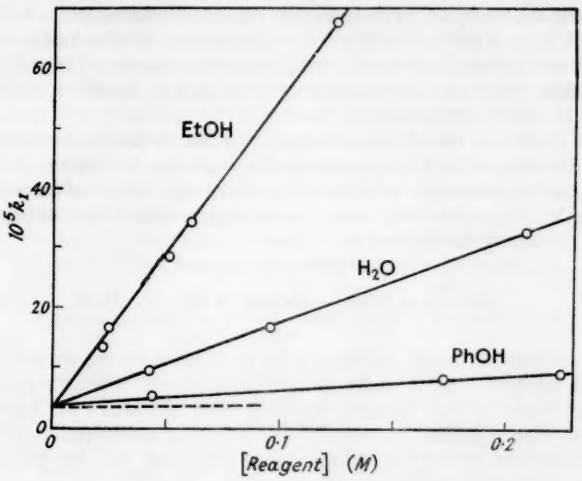
The lower sections of Table 6 record some rate-constants for the total reactions which were observed when various pairs of substituting agents were acting together. The

adjacent figures labelled " Calc." are the corresponding rates as calculated from equation (5) :

$$k_1 = k_1^{ROH} + k_1^{R'OH} - 4{\cdot}0 \times 10^{-5} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where ROH, R'OH = HOH, EtOH, PhOH. The general agreement between the observed and the calculated rates allows us to conclude that, over the investigated range of reagent concentrations, the rate-constant of the total reaction of triphenylmethyl chloride with

FIG. 4. *First-order rate-constants for reactions of triphenylmethyl chloride in the presence of pyridine in nitromethane at 0·0°, as functions of the concentrations of the substituting agents.*



any mixture of the three substituting agents could be calculated from an additive expression without " mutual " terms :

$$10^5k_1 = 4{\cdot}0 + 125\,[H_2O] + 500\,[EtOH] + 25\,[PhOH] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

DISCUSSION

(3) *Reactions of* tert.-*Butyl Bromide : Electrophilic Catalysis of Ionisation.*—The observations presented in Section (1) leave no doubt that all the investigated reactions of *tert.*-butyl bromide in nitromethane, *i.e.*, the elimination, and the three substitutions with hydroxylic substituting agents, follow the familiar $E1$ and S_N1 mechanisms. The first-order kinetics, the fact that the products can be changed without a change of rate, and the observed ionic strength and mass-law effects, all point to this conclusion. The essential function of the pyridine in all these reactions seems only to be that it allows them to go much further forward, by replacing the formed hydrogen bromide by the more weakly acidic pyridinium ion.

We have, then, basically, two-stage processes, the first stage rate-controlling, and the second product-forming. For substitution they may be represented thus :

$$Bu^tBr \xrightarrow[Slow]{} \{Bu^t\}^+Br^- \xrightarrow[Fast]{ROH} Bu^tOR + H^+\text{-pyridine} + Br^- \quad . \quad . \quad . \quad . \quad (S_N1)$$

Against this background, it has to be considered why large concentrations of the substituting agents increase the first-order rate, the increases being linear over considerable ranges of reagent concentration. The linear curves in Fig. 3 are of a kind which Bird, Hughes, and Ingold looked for, but did not find, in their work on the Menschutkin reactions of *m*-chlorobenzhydryl chloride (*J.*, 1954, 634); and, as is shown by their discussion of the

observed, more complicated kinetic relations, the essential meaning of the present linear curves must be that *one* molecule of the reagent is involved *at close range* in the transition states of the rate-controlling processes. The absence of "mutual" terms from the equation for the rates with mixtures of substituting agents (equation 3) confirms the conclusion that only one hydroxylic molecule is involved.

Now this strictly kinetic conclusion might be chemically specialised in either of two possible ways. One trial specialisation would be that, superposed on the S_N1 substitution, an S_N2 substitution is taking place, or, in other words, that in some of the individual molecular acts of substitution, the substituting agent is attacking the carbon end of the breaking carbon–halogen bond. But, if this were true, the order in which the substituting agents should stand with respect to their kinetic effects should be the order of their nucleophilic power, EtOH > HOH > PhOH, *i.e.*, the inverse of the order of their acidity. Actually, as is shown in Fig. 3, or by the coefficients in equations (1) and (3), the reagents stand in the opposite order, *i.e.*, in the order of their acidity, EtOH < HOH < PhOH, the relevant coefficients being in the ratios 1 : 2 : 5·5.

This makes it clear that the alternative specialisation is the correct one: the hydroxyl compounds are intervening in the rate-controlling process by virtue of those structural features which make them acids: in some of the transition states of ionisation of the alkyl halide, they are hydrogen-bonding with the halogen, and thus assisting the electron transfer and the covalency disruption:

$$\mathrm{Bu^t{-}Br} + \mathrm{HOR} \xrightarrow[\text{Slow}]{} \mathrm{Bu^{t+}} + \mathrm{Br^-} \ldots . \mathrm{HOR}$$

The hydrogen-bonding, although electrostatic, is a short-range interaction, and hence must produce an integral kinetic order, unlike interactions of longer range in which the positional requirements of the reagent are less well defined. To summarise, we are observing here an electrophilic catalysis of unimolecular nucleophilic substitution, quite similar to that described before for strongly acid catalysts, and for catalysing silver and mercuric ions in hydroxylic media.

Within the range of the linear kinetic effects, no hydroxylic molecule other than that just discussed can be involved in any way in the transition state of ionisation: its solvation shell must consist (as we hoped when choosing nitromethane for solvent) exclusively of nitromethane molecules. But water is peculiar in that a more-than-linear acceleration sets in when its concentration exceeds 0·5M, such extra acceleration affecting the total reaction of the alkyl halide, even though a part of that reaction may end by involving a substituting agent other than water. We ascribe this extra acceleration to a macroscopic solvent effect. Water is more solvating than either of the other two hydroxyl compounds, and, when a solvent, is much more strongly ionising. Thus it is to be expected that, when its volume concentration reaches units per cent., occasions will arise in which a molecule of water, or even more than one, intrudes among the nitromethane molecules in the general solvation shell of a transition state. The fact that we find this effect with water, which, whilst it is outstanding as a polar solvent, is neither the most acid nor the least acid of the three hydroxy-compounds, supports this interpretation.

(4) *Reactions of Triphenylmethyl Chloride: Fast Ionisation and a Slow Subsequent Step.*—It has been found by other workers in these laboratories that triphenylmethyl chloride in nitromethane undergoes halide-ion exchange immeasurably rapidly. We also have optical evidence that triphenylmethyl chloride in nitromethane establishes equilibrium with its ions practically instantaneously. Thus, there can be no doubt that the ionisation of triphenylmethyl chloride in nitromethane occurs extremely readily, and that the carbonium ion is instantly and unrestrictedly available to any reaction requiring it.

With reference to the kinetic studies, described in Section 2, of the reactions of triphenylmethyl chloride in the presence of pyridine with hydroxylic substituting agents in nitromethane, it follows from the above considerations that, if we try to build a reaction scheme based on ionisation, employing the usual two stages of the unimolecular mechanism of substitution, we cannot make the ionisation stage rate-controlling. But, in view of the

outstanding thermodynamic stability of the triphenylmethylium ion, we might try to make rate-controlling its interaction with the substituting agent.

Support is given to this idea by the absence of salt effects. That shows that the rate is not controlled by the ionisation of a neutral molecule, and, furthermore, that it is controlled by a process having the same number of ionic charges on both sides of the chemical equation.

Further support for the same outlook may be derived from the linear accelerations observed with the higher concentrations of substituting agents. The linearity of these effects, and the absence of "mutual" terms from the rates given by mixtures of the substituting agents (equation 6), prove that only one hydroxylic molecule is involved in the rate-controlling process. Now, as can be seen in Fig. 4, and by the coefficients in equations (4) and (6), the order in which the three substituting agents stand with respect to these kinetic effects is just the reverse of the order found for the reactions of *tert.*-butyl bromide. The present order is neither that of the acidities of the reagents, nor that of their ionising power, but it is that of their nucleophilic power, EtOH > HOH > PhOH: the kinetic coefficients diminish along this series in the ratios 20 : 5 : 1. When these substituting agents attack a *pre-formed* cation, they can only do so as nucleophilic reagents, and our hypothesis that such an attack controls the measured rate requires that the accelerating effects should stand in this order.

If we now try to set up the type of mechanism considered in its simplest conceivable form, *i.e.*, as an S_N1 mechanism, except for a reversed order of rates,

$$Ph_3Cl \underset{\text{Fast}}{\rightleftharpoons} Ph_3C^+ + Cl^- \xrightarrow[\text{Slow}]{\text{ROH}} Ph_3C{\cdot}OR + H^+\text{-pyridine} + Cl^-$$

we see at once that, in this form, it is inadequate for the following reasons. First, it does not account for the instantaneous discharge of the colour of the carbonium ion when pyridine is added to a solution of triphenylmethyl chloride in nitromethane. It thus appears that pyridine forms a complex almost instantaneously with the carbonium ion. Secondly, as the second and fast step in an ordinary unimolecular non-solvolytic substitution is bimolecular, so we have written the above second and slow step as bimolecular; and thus the above mechanism does not allow for the fact that, with low concentrations of substituting agents, the overall reaction is essentially of first-order.

These difficulties disappear if we include the complexing of the carbonium ion with pyridine in the fast preliminary process, as follows:

$$Ph_3CCl \underset{\text{Fast}}{\rightleftharpoons} Ph_3C^+ + Cl^- \xrightarrow[\text{Fast}]{\text{Pyridine}} Ph_3C{\cdot}\overset{+}{N}C_5H_5 + Cl^-$$

$$Ph_3C{\cdot}\overset{+}{N}C_5H_5 \xrightarrow{\text{Slow}} Ph_3C^+ + NC_5H_5 \xrightarrow[\text{Fast}]{\text{ROH}} Ph_3C{\cdot}OR + H\overset{+}{N}C_5H_5 \quad \text{(1st order)}$$

$$Ph_3C{\cdot}\overset{+}{N}C_5H_5 \xrightarrow[\text{Slow}]{\text{ROH}} Ph_3C{\cdot}OR + H\overset{+}{N}{\cdot}C_5H_5 \quad \text{(2nd order)}$$

All the qualitative and kinetic observations are accommodated in this scheme, and we think that they are sufficiently varied and extensive to allow us to regard it as well-founded. It follows from it, that the use of a stronger complexing agent than pyridine should lead to diminished rates of reaction with the hydroxyl compounds; and we have verified that, on replacement of pyridine with triethylamine, these reactions are, indeed, rendered too slow for measurement.

(5) *Functions of Hydroxylic Molecules in Solvolytic and Non-solvolytic Substitutions with Hydroxylic Reagents.*—The deductions of Sections 3 and 4 are probably all that, strictly logically, we should draw. Yet, although our experiments relate to non-solvolytic reactions, they do offer suggestions as to what specific functions hydroxylic molecules may assume in the solvolytic substitutions of alkyl halides, in addition to the general function of providing a solvating medium. Similarly, our results suggest by what molecular

processes kinetics may be determined in reactions of alkyl halides with hydroxylic molecules in less polar solvents than nitromethane, and even, by a long extrapolation, in non-polar solvents.

Taking as basis the separate chemical processes involved in S_N1 and S_N2 substitutions,

$$\mathrm{AlkX} \xrightarrow[(1)]{} \mathrm{Alk^+ + X^-} \xrightarrow[(2)]{\mathrm{ROH}} \mathrm{AlkOH + HX}$$

$$\mathrm{ROH + AlkX} \xrightarrow[(3)]{} \mathrm{AlkOR + HX}$$

we can envisage three well-defined mechanisms, as set out below, although transitional situations between the first and second, and between the second and third, are obviously possible:

S_N2C^+ . . . . (1) fast, (2) slow (Alk^+, possibly complexed, long life)
S_N1 . . . . . (1) slow, (2) fast (Alk^+, short life)
S_N2 . . . . . infinitely fast (2) merges with (1) in (3) (Alk^+, no life)

The first of these has hitherto been less fully considered than the others, but a large field for it exists in *pseudo*-base chemistry, *e.g.*, in slow basifications of rapidly ionising *pseudo*-salts.

The ways in which a hydroxylic molecule, whether solvent or solute, might enter the rate-controlling steps of these processes are as follows:

S_N2C^+, as nucleophilic substituting agent, and by a general solvent effect;
S_N1, as electrophilic catalyst, and by a strong general solvent effect;
S_N2, as nucleophilic substituting agent, and as electrophilic catalyst, and also by a general solvent effect.

In solvolysis, the functions listed will determine rate, but not kinetic order, and thus, as we have pointed out before, less direct methods than the determination of kinetic form have to be applied in seeking to distinguish them.

In substitution conducted non-solvolytically, the various modes of action of the hydroxylic reactants could give rise to the following kinetic orders, which are here additively itemised in the sequence of the reagent functions set out above:

S_N2C^+ . . . . Order $= 1 + s$ or $2 + s$
S_N1 . . . . . Order $= 1 + 1 + S$
S_N2 . . . . . Order $= 2 + 1 + s$

The point of the itemisation is that (as has been illustrated in this paper) the onset of the different contributions to the observed total order may become appreciable at different concentrations of the hydroxy-compound. The symbols S and s stand for any apparent order, often non-integral, arising from a general co-solvent function. It might be unobservable. Its importance for the two well-known mechanisms should follow the sequence $S_N1 > S_N2$. It should be more important in weakly polar than in strongly polar solvents.

Swain and his co-workers (*J. Amer. Chem. Soc.*, 1948, **70**, 1119, 2989; 1950, **72**, 2794; 1951, **73**, 2813) have studied the reactions of several alkyl halides with hydroxylic reagents in solvent benzene, and have carried over conclusions, drawn from results obtained in such conditions, directly to the problems of solvolysis—a dubious proceeding in itself, but one which can, we think, be made somewhat more secure by the use of results for polar aprotic solvents, such as nitromethane, as a stepping-stone. One sees from the above statement of possible reaction orders, that Swain's observation of orders of 3 does not necessitate the conclusions which were drawn, *viz.*, that what we have classified as the bimolecular and unimolecular mechanisms of nucleophilic substitution are identical, and are one-stage termolecular processes. When a solvent is made less polar, until it finally becomes non-polar, the mechanism itself is expected to shift in the direction $S_N2C^+ \longrightarrow S_N1 \longrightarrow S_N2$. Mechanism S_N1, supposing that, for some particular alkyl halide, any mechanistic change

did not go beyond that point, might build up an overall order of 3 with the aid of its large co-solvent effect. Mechanism S_N2, intrinsically more probable in a fully non-polar solvent, could hardly fail to give an order of 3 at lower reagent concentrations than would bring in a general co-solvent effect. These explanations, the second of which, already offered by Hughes (cf. Ingold, "Structure and Mechanisms in Organic Chemistry," Cornell Univ. Press, 1953, p. 356), is preferred, assume no reagent function which was not illustrated by us in or before 1940.*

Experimental

Materials.—Nitromethane, dried with calcium chloride, and, after refluxing under nitrogen, with magnesium perchlorate, was fractionally distilled, the middle one-third, b. p. 100·3—100·5°, being accepted. As used in the kinetic experiments, it had a water content, estimated by the Karl Fischer method, of less than 0·02%. "AnalaR" phenol was crystallised from light petroleum, while *tert.*-butyl bromide, triphenylmethyl chloride, ethyl alcohol, pyridine, tetraethylammonium chloride and bromide, and the acetone used in the analytical procedure, were purified by methods which have been described in papers from this laboratory. Carbonate-free standard sodium hydroxide was checked periodically against constant-boiling hydrochloric acid.

Kinetic Measurements.—For most of the runs, reaction mixtures, made up to 50 c.c. in glass-stoppered flasks, were prepared, either by direct weighing, or by the previous preparation by weighing of separate standard solutions in nitromethane of the reactants, which were mixed with the aid of automatic pipettes (error $\pm$ 0·02%). Thermostats were set to 0°, 25°, and 40° to within $\pm$0·02°. Aliquots of 5 c.c., withdrawn by means of an automatic pipette, attached to the flask, jacketted with the thermostat liquid as necessary, and operated by pressure of dry nitrogen, were delivered into 70 c.c. of acetone at 0°, and titrated with aqueous sodium hydroxide using lacmoid as indicator.

Some of the runs at 40° were conducted by the sealed-tube method, but rather as a check upon the standard method than as a necessity. Determinations of acid were in some cases checked by determinations of halide ion. Initial concentrations of alkyl halide, as given by weighing, were checked against the final titres, and in some cases also by decomposing an aliquot portion with aqueous acetone, and subsequently measuring either the acid or the halide ion. All these checks were satisfactory. Rate constants for the reactions of *tert.*-butyl bromide are probably good to $\pm$2—3%, whilst those for the faster reactions of triphenylmethyl chloride are rather less reliable.

Products.—The method of examination is indicated, and an example is given, at the end of Section 1.

This paper has benefited considerably from discussions with Dr. P. B. D. de la Mare and Dr. Y. Pocker, whom we thank.

William Ramsay and Ralph Forster Laboratories,
University College, Gower St., London, W.C.1. [*Received, April 12th,* 1954.]

* We have used the past tense in referring to Swain's conclusions, since it is not quite clear whether or not they are still maintained. Swain, Scott, and Lohmann (*J. Amer. Chem. Soc.*, 1953, **75**, 136) recently observed large common-ion retardations, as well as strong non-common-anion interventions without rate-change, in the aqueous solvolysis of triphenylmethyl halides; and they explained these phenomena exactly as we would explain them. However, the brevity of their paper did not permit them either to refer to our precisely similar demonstrations and conclusions of 1940 relating to benzhydryl halides, with an explicit prediction of similar effects for triphenylmethyl halides, or to discuss the bearing of their new results on the previous conclusions of Swain already mentioned.

Mechanism of Substitution at a Saturated Carbon Atom. Part XL. Unimolecular Nucleophilic Substitution and Elimination of* tert.*-Butyl Bromide with Anionic Reagents in Nitromethane Solvent; with some Remarks on the Addition of Acids to Olefins.*

By P. B. D. de la Mare, E. D. Hughes, C. K. Ingold, and Y. Pocker.

[Reprint Order No. 5298.]

The reactions of *tert.*-butyl bromide with bromide ions, with chloride ions, and with nitrite ions have been studied kinetically in nitromethane solution. The reaction with bromide ions is stoicheiometrically mainly one of substitution, though strongly reversed elimination occurs concurrently. The reaction with chloride ions is mainly one of elimination, which is much less strongly reversed. The reaction with nitrite ions consists of two substitutions, together with an elimination. The total reactions in all these cases are of first order in the alkyl bromide, and of zero order in the anionic reagent. The reactions show a positive salt effect, but their absolute rates at low reagent concentrations are almost identical with one another and with common limiting rate of the reactions of *tert.*-butyl bromide in nitromethane with pyridine, and with the hydroxylic reagents, examined in the preceding paper. It is concluded that all these reactions of substitution and elimination have the unimolecular mechanism.

The additions of hydrogen bromide and of hydrogen chloride to *iso*-butylene in nitromethane are retarded by bromide ions and by chloride ions, respectively. It is inferred that the halogen acids cannot as such protonate the olefin, but must first set their protons relatively free in pre-equilibrium. An extension of this conclusion to the acid hydration of olefins in aqueous solution is considered.

The nature of the unimolecular mechanism of nucleophilic substitution and elimination has long been a subject of controversy, partly for the reason that the first investigations of it (1933—1940) related mainly to solvolytic substitution, for which the most elementary kinetic criterion of mechanism is unavailable. Therefore special interest attaches to the study of the unimolecular mechanism in those aprotic solvents which are polar enough to sustain it. Here we continue the study of the substitution and elimination reactions of *tert.*-butyl bromide in solvent nitromethane. The simple idea of the investigation is that which was applied in the first work of this kind in solvent sulphur dioxide (*J.*, 1940, 1011), *viz.*, that in the unimolecular mechanism all nucleophilic reagents should react with a common substrate at the same rate, whereas in the bimolecular mechanism they should react at very different rates. We know (preceding paper) the rates at which *tert.*-butyl bromide undergoes unimolecular elimination through the action of pyridine, and unimolecular substitution with the reagents, water, ethyl alcohol, and phenol, in solvent nitromethane. We now report on its reactions with bromide ions, chloride ions, and nitrite ions in that solvent. Our investigation has so developed that it bears not only on the mechanism of unimolecular substitution and elimination, but also on that of the reversal of the latter process in the addition of acids to olefins.

(1) *Reactions of* tert.*-Butyl Bromide with Bromide Ion.*—These reactions were studied over a range of temperature, and for one temperature over a range of reagent concentrations, the basic measurement being that of isotopic exchange between ordinary bromine of *tert.*-butyl bromide and bromine made radioactive with ^{82}Br of half-life 36 hr., supplied in the form of tetraethylammonium bromide. The results are in Table 1. They are calculated by a method (p. 2938) which allows for radioactive decay and dilution, and for any reaction which occurs during warming to the reaction temperature, as well as for the concomitant expansion of the solvent. The counting rates C, $C - X_1$, and $C - X_2$ measure specific radioactivities of the tetraethylammonium bromide, initially, at a time t_1

* Part XXXIX, preceding paper.

soon after the solution has attained reaction temperature, and at a later time t_2, respectively. The spread of the calculated first-order rate constants, k_1, for each temperature and reagent concentration, is typical of such experiments, and arises almost entirely from random fluctuations in counts measured within finite time intervals. Usually counts of about 10,000 were recorded on each sample, and it can be computed that this number should lead to a probable error of 3% in resulting rate-constants. The fact that the standard deviation in all the groups of more than three rate-constants lies in the range 4·2—5·6% (corresponding to a formal probable error of 2·8—3·7%) shows that no other casual kinetic errors are of comparable importance.

The near-identity of mean rate-constants at a fixed temperature, when the reagent concentration is varied, shows that the recorded first-order constants are indeed measuring unimolecular reactions.

TABLE 1. *Rate constants (k_1 in sec.$^{-1}$) of bromine exchange between* tert.*-butyl bromide and tetraethylammonium radio-bromide in nitromethane.*

Temp.	[Bu^{t}Br]	[NEt$_4$Br]	Counting rates C	Counting rates $C-X_1$	Counting rates $C-X_2$	$t_2 - t_1$ (min.)	$10^5 k_1$	$10^5 k_1$, mean
49·7°	0·0511	0·0220	1191	1142	988·3	29·7	6·12	
					903·8	35·5	6·49	
					853·3	45·6	6·60	6·54
					767·9	49·7	6·54	
					698·1	60·2	6·96	
40·6	0·0466	0·0479	382·8	387·6	318·4	122·2	3·03	
					322·8	124·7	2·74	2·88
					305·6	161·4	2·87	
40·6	0·0470	0·0239	382·8	393·0	235·9	193·3	2·56	
					233·0	197·5	2·59	2·56
					234·4	200·2	2·52	
40·6	0·0470	0·0120	382·8	380·6	220·4	106·9	2·45	2·62
					114·9	257·3	2·80	
40·5	0·0488	0·0243	1012	1020	780·2	91·5	2·60	
					744·0	123·0	2·31	2·51
					685·3	143·0	2·59	
					589·6	206·0	2·66	
25·0	0·0497	0·0248	409·3	406·0	255·8	997·0	0·452	
					259·6	1013	0·428	
					262·1	1015	0·416	
					244·3	1031	0·492	0·448
					250·3	1050	0·454	
					251·3	1057	0·447	
21·7	0·0529	0·0228	571·5	566·7	336·2	1448	0·305	
					318·6	1548	0·321	
					327·3	1646	0·284	0·298
					323·5	1706	0·282	
					306·3	1766	0·306	

With the aid of unpublished work by P. J. C. Fierens, and by one of us (P. B. D. de la M.) on bimolecular halogen exchanges in acetone and in nitromethane, we can derive further support for this conclusion from solvent effects on reaction rate. The bromide-ion exchanges of primary alkyl halides are bimolecular, both with lithium bromide in acetone and with tetraethylammonium bromide in nitromethane; and reaction in the latter, more polar, solvent is appreciably the slower, as we should expect from the theory of kinetic solvent effects for a bimolecular reaction of this charge-type. Thus for *n*-propyl bromide, reacting at 25°, with a salt concentration 0·024M, the second-order rate-constants are 108×10^{-5} sec.$^{-1}$ mole^{-1} l. in acetone, and 24×10^{-5} sec.$^{-1}$ mole^{-1} l. in nitromethane. For the reaction of *tert.*-butyl bromide with lithium bromide in acetone, the second-order rate-constant can also be determined: in similar conditions, this rate-constant has the value $0{\cdot}52 \times 10^{-5}$ sec.$^{-1}$ mole^{-1} l. A bimolecular reaction of *tert.*-butyl bromide with tetraethylammonium bromide in nitromethane should be slower: the comparable rate-constant would be of the order of $0{\cdot}1 \times 10^{-5}$ sec.$^{-1}$ mole^{-1} l. In fact, the absolute rate of the reaction of *tert.*-butyl bromide in nitromethane is much greater, its rate-constant for the above conditions, computed as a second-order constant for comparison, being

18×10^{-5} sec.$^{-1}$ mole^{-1} l. This would be expected if, in the highly polar solvent, the slow bimolecular substitution is being overlaid by a much more rapid unimolecular exchange.

The temperature dependence of the rate of the *tert.*-butyl bromide exchange in nitromethane satisfies the equation $k_1 = Be^{-E/RT}$ sec.$^{-1}$, with the substitutions $\log_{10} B = 9{\cdot}76$ and $E = 20{\cdot}6$ kcal./mole, values to which we shall refer in Section (4).

Table 1 contains an indication, in the results of experiments at 40·6°, of an increase in the rate of exchange with increasing concentration of the ionic bromide. This effect is in excess of the experimental error. It can be classed as a salt effect, as we shall see in more detail in Sections (2) and (4).

It has been shown that, although the stoicheiometric reaction is essentially one of substitution, concurrent elimination occurs: the latter process has been followed by measuring the development of acidity. Initially, acid is formed at nearly the rate of the bromide exchange; but the amount of acid ultimately developed is quite small. Thus at 25·0°, for which the rate constant for bromide exchange is $0{\cdot}448 \times 10^{-5}$ sec.$^{-1}$ and represents 50% of conversion in 14·3 hr., the rate of development of acid during the first 15 min. was about $0{\cdot}41 \times 10^{-5}$ sec.$^{-1}$; but within 2 hr. the rate had fallen to zero; and the total amount of acid formed, by then 1%, thereafter remained constant. The obvious conclusion is that *iso*butylene adds hydrogen bromide rapidly and almost completely in these conditions; and this has been directly confirmed. In a solution, made up at 25° to contain 0·0174M-*iso*butylene and 0·0126M-hydrogen bromide, the additive process reached 98% of completion in 2·5 min. and 99·4% in 30 min.; and it later attained completion to within the analytical error. The addition was, however, retarded by the presence of tetraethylammonium bromide. Thus, in an experiment closely comparable to that just mentioned, except that the salt was also present in 0·02M concentration, the addition process reached 98% of completion only after 3 hr.; and the ultimate extent of reaction was only 99·4%. This kinetic effect can be interpreted as a repression, by the added bromide ions, of the ionisation of hydrogen bromide, and thus of the production of protons in a sufficiently free condition to be accepted by the olefin. In other words, we assume that the covalent acid HBr cannot as such protonate the olefin, but must first set its proton relatively free in pre-equilibrium. In the absence of definite knowledge as to just what the free state is, we shall write it in equations given later in the simple form H^+. As will be noted in Section 2, chloride ions have a similar repressing effect on the addition of hydrogen chloride to *iso*butylene, and we interpret this similarly.*

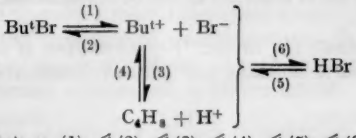
It is interesting to compare these results and conclusions with Taft's result (*J. Amer. Chem. Soc.*, 1952, **74**, 5372) that the rate of acid hydration of olefins in aqueous solution follows Hammett's acidity function rather than the hydrogen-ion concentration, and with his conclusion, derived therefrom, that the adding proton must first leave the covalent acid H_3O^+, and get into some more available condition in pre-equilibrium, before it can participate in the slow process of forming the carbonium ion. If we leave aside the special form in which Taft cast his interpretation (he assumed slow isomerisation of a π-bond complex), it is, in its essentials, similar to that which we have given for acid addition to an olefin in our aprotic solvent. The correspondence suggests that, even in aqueous solution, there may possibly be some freer form of protons than the normal electronic state of covalent H_3O^+. Pending further clarification, we could write this freer form simply as H^+, thereby obtaining a system of chemical equations for the acid hydration of olefins, which, whilst they omit unproved details, do express the kinetic findings:

$$H_3O^+ \overset{\text{Fast}}{\rightleftharpoons} H_2O + H^+ \qquad \text{Olefin} + H^+ \overset{\text{Slow}}{\rightleftharpoons} \text{Carbonium ion}$$

To return to the reactions in nitromethane, we have already concluded that the mechanism of the substitution process is unimolecular, and therefore no critical question of mechanism is raised by the observation that *iso*butylene is simultaneously produced in low concentration, but at an initial rate nearly equal to the steady rate of substitution. The consistent interpretation is that the elimination, like the substitution, is part of the total

* The results cited are taken from a more general study soon to be reported, of the kinetics of the addition of acids to olefins in aprotic solvents.

unimolecular process, the carbonium ion, formed in the common rate-controlling stage, undergoing relatively rapid, but strongly reversible, proton loss, besides back-conversion with bromide ions into the alkyl bromide. By adding to this our conclusion that the reversal of the elimination depends on prior proton loss from hydrogen bromide, the complete system of equations may be represented as follows :



[Rates : (1) ≪ (2) ≪ (3) ≪ (4) ≪ (5) ≪ (6)]

We have, for kinetic reasons, to describe the formation of the olefin as dependent on unimolecular proton-loss by the carbonium ion, and not on bimolecular extraction of the proton by a bromide ion; and, for independent kinetic reasons, we have had to describe the protonation of the olefin as being effected by previously liberated protons, and not by direct attack of the proton-carrier, hydrogen bromide. Actually these two conclusions are correlated by theory, and either could have been deduced from the other by the principle of microscopic reversibility.

(2) *The Reactions of* tert.*-Butyl Bromide with Chloride Ion.*—These reactions were studied at one temperature only, 25·0°. The chloride ion was supplied as tetraethylammonium chloride. The kinetics of the reactions which ensued were more involved than those of the reactions just described, but when unravelled showed that the reactions with chloride ion follow quite similar mechanisms. The main difference is that the elimination, which was a minor reaction before, now constitutes the main part of the process. Thus, after the commencement of reaction, both hydrogen bromide and hydrogen chloride are present in quantity, and it is this which produces the more complex kinetics.

The kinetics were studied in four ways : (*a*) by following the development of bromide ion, which measures substitution plus elimination, (*b*) by following the production of acid, which measures the elimination only, (*c*) by determination of chloride ion, which should isolate the substitution, and (*d*) by determination of the formed *iso*butylene, which provides a direct check on the amount of elimination. The bromide and chloride ions were separately determined by electrometric titration, the acid by titration with alkali, and the *iso*butylene by its uptake of bromine.

When the rate of the total reaction, as measured by bromide-ion development, was expressed as first-order rate constants, these were found to remain steady over the first 10% of reaction, but thereafter to fall away. Because of the mathematical difficulties involved in elucidating a system of interlocked reactions on the basis of the precise forms of drift shown by drifting rate-constants, it was decided to study in detail only the initial steady period of reaction by various methods, and in various sets of initial conditions.

During this initial period, the bromide-ion concentration rises, but the chloride-ion concentration does not fall comparably, while the acid concentration, and equally the olefin concentration, both rise nearly as rapidly as does the concentration of bromide ions. This is illustrated by the three runs compared in Table 2, from which it appears that at least 90% of the initial reaction consists of elimination. It was confirmed that no elimination is apparent in the absence of tetraethylammonium chloride.

Despite the need for tetraethylammonium chloride, the rates of reaction depend only slightly on its concentration, within the range of our experiments. This is shown both for bromide-ion development, and for acid production, in Table 3. In the measurements on bromide ions, the concentration of tetraethylammonium chloride could not be taken up to very high values, because the determination of bromide ion in the presence of the chloride ion then becomes too inaccurate. However, the rates are seen to rise by only 30% for a 3-fold increase in the concentration of the chloride. The measurements of acid involve no such analytical difficulty, and accordingly the concentration of supplied chloride was taken

up to relatively high values. The rate now increased 3½ times for a 29-fold increase in the concentration of chloride.

In considering the kinetic situation revealed by the results described, it is convenient at first to neglect as a detail the slow variations of rate with changing concentration of the tetraethylammonium chloride: it is a point to which we shall return. Such details apart, our conclusions are that the main reaction is one of elimination, that it becomes observable

TABLE 2. *Initial rate-constants (k_1 in sec.$^{-1}$) of formation of bromide ions, hydrogen ions, and olefin, from* tert.*-butyl bromide and tetraethylammonium chloride in nitromethane at 25·0°.*

Run	$[Bu^tBr]_0$	$[NEt_4Cl]_0$	Method	10^5k_1
86	0·0202	0·0204	$d[Br^-]/dt$	0·56
87A	0·0202	0·0200	$d[H^+]/dt$	0·52
87B	0·0202	0·0200	d[Olefin]/dt	0·51

TABLE 3. *Initial rates (k_1 in sec.$^{-1}$) of production of bromide ions, and of hydrogen ions, from* tert.*-butyl bromide in nitromethane at 25·0°, as a function of the concentration of added tetraethylammonium chloride.*

Run	$[Bu^tBr]_0$	$[NEt_4Cl]_0$	Method	10^5k_1
83	0·0200	0·0110	$d[Br^-]/dt$ *	0·45
84	0·0200	0·0128	,, *	0·48
86	0·0202	0·0200	,, †	0·56
81	0·0197	0·0290	,, *	0·60
29A	0·0200	0·0049	$d[H^+]/dt$	0·40
8A	0·0201	0·0111	,,	0·45
87A	0·0202	0·0200	,,	0·52
7A	0·0202	0·0506	,,	0·74
6A	0·0200	0·0730	,,	0·89
18A	0·0200	0·0983	,,	1·10
19A	0·0200	0·1410	,,	1·43

* Extraction method (cf. p. 2938). † Evaporation method (cf. p. 2938).

only in the presence of the tetraethylammonium chloride, but that its rate is approximately independent of the concentration of that reagent. These conclusions can only be reconciled on the assumption that the elimination is unimolecular, depending for its rate on that of the ionisation of the *tert.*-butyl bromide, and that the tetraethylammonium chloride acts by retarding the retrograde reaction of addition to the formed olefin. Certainly it might be expected to do so. We know that, under our experimental conditions, hydrogen bromide adds to *iso*butylene rapidly and almost completely. The expected first effect of the tetraethylammonium chloride would be to replace most of the formed hydrogen bromide by less ionising, and presumably less rapidly adding, hydrogen chloride. And a supporting second effect is expected: for, just as the rate of addition of hydrogen bromide to *iso*butylene is depressed in the presence of bromide ions, so the presumably smaller rate of addition of hydrogen chloride should be further reduced by the presence of chloride ions. These retarding effects could allow the elimination to go forward a considerable distance, but still at a rate essentially controlled by that of the ionisation of the alkyl bromide.

The general validity of this interpretation has been checked by a direct examination of the rate of addition of hydrogen chloride to *iso*butylene in nitromethane, in the absence, and in the presence of added tetraethylammonium chloride. In our conditions, hydrogen chloride, in the absence of added salt, adds to *iso*butylene some hundreds of times more slowly than does hydrogen bromide, though ultimately the addition goes almost to completion. In the presence of 0·02M-tetraethylammonium chloride, the rate of addition of hydrogen chloride is reduced by a further factor of a similarly large order. Two runs are recorded for illustration in Table 4: they were followed by measuring the disappearance of acid.

Returning to the slow increase in the rate of elimination with increasing concentration of tetraethylammonium chloride, it is easy to exclude the hypothesis that this is connected with the increased suppression by this salt of the back-reaction of addition of halogen-acids to the olefin. For first, the observed rates are initial rates. And secondly, an upper limit

to the possible effect of reducing the additive reactivity of hydrogen halides can be set by removing them completely, by the addition, not of tetraethylammonium chloride, but of pyridine, or triethylamine. However, as the preceding paper shows, the rate of elimination in the presence of excess of pyridine ($k_1 = 0{\cdot}39 \times 10^{-5}$ sec.$^{-1}$ at 25·0°) is not above the lowest of the rates recorded in Table 3 (run 29A) for elimination in the presence of tetraethylammonium chloride, and is therefore very far from being an upper limit to a range of rates which run up to values more than three times higher. A similar statement holds for the reaction in the presence of triethylamine. We can almost as definitely excluded the hypothesis that the slow increase of rate with increasing salt concentration arises from a minor bimolecular component of the reaction. If any of the investigated

TABLE 4. *Rate of addition of hydrogen chloride to* iso*butylene in nitromethane at* 25·0° *in the absence and in the presence of tetraethylammonium chloride.*

Run 2A: Initially, $[C_4H_8] = 0{\cdot}017$M; [HCl] = 0·0169M; $[NEt_4Cl] = 0{\cdot}0000$M.				*Run* 4A: Initially, $[C_4H_8] = 0{\cdot}0210$M; [HCl] = 0·0207M; $[NEt_4Cl] = 0{\cdot}0200$M.			
t (min.)	HCl (%)	*t* (min.)	HCl (%)	*t* (min.)	HCl (%)	*t* (min.)	HCl (%)
0	100	150	20·2	0	100	150	93·9
30	41·5	180	17·6	30	99·0	180	92·8
60	32·7	210	16·4	60	97·9	1440	75·5
95	26·4	270	12·6	90	95·9	2880	66·3
120	22·6	1260	1·9	120	94·9		

eliminations of *tert.*-butyl bromide could show a bimolecular component, the reactions with amines should do so. Yet it was noted in the preceding paper that the rate of elimination in the presence of pyridine is independent of the concentration of pyridine up to 0·11M; and the same point has been verified for elimination in the presence of triethylamine over the concentration range 0·01—0·06M. Therefore, we conclude that the slow rate change with increasing salt concentration represents a long-range interaction, classifiable as a salt effect. We shall refer to it again in Section (4).

The remaining detail of the kinetics of the reaction of chloride ions with *tert.*-butyl bromide relates to the minor process of substitution; but, as to this, we cannot make any precise statement from direct observation, for the reason that there is too little substitution to be treated accurately by the not very exact techniques available for determining chloride and bromide ions in the presence of each other in our reaction system. Our conclusions concerning this part of the reaction rest on analogy with the bromide-ion reaction. This granted, a scheme can be written for the chloride-ion reaction which is similar to that given on p. 2933, except for the complication of including chloride ion and hydrogen chloride, and the changes in relative rates already discussed.

(3) *Reactions of* tert.*-Butyl Bromide with Nitrite Ion.*—The nitrite ions were supplied as either tetraethyl- or tetramethyl-ammonium nitrite, and the rate of the total reaction, as given by electrometric titration of the formed bromide ions, was studied for a range of salt concentrations at one temperature, and for a range of temperatures at one salt concentration.

A qualitative examination of the reaction product showed that substitution and elimination were both taking place. There were two substitution products, *tert.*-nitro*iso*butane and *tert.*-butyl nitrite. The elimination product was *iso*butylene. At a later stage of these primary reactions, the *tert.*-butyl nitrite, and the formed bromide ion, began to disappear, and some nitrosyl bromide was produced. The *tert.*-nitro*iso*butane, once formed, underwent no further reaction. In the following summary of these chemical changes, it is assumed, though it was not directly proved, that *tert.*-butyl alcohol is produced along with the nitrosyl bromide: *

$$Bu^tBr \xrightarrow[NO_2^-]{} \left\{ \begin{matrix} Br^- + Bu^tNO_2 + Bu^tO{\cdot}NO \\ (CH_3)_2C{:}CH_2 + H^+ + Br^- \end{matrix} \right\} \longrightarrow Bu^tOH + NOBr$$

It was found that the first 80% of the primary reactions, which liberate bromide ions from *tert.*-butyl bromide, could be kinetically followed, without interference from the

* We are still uncertain whether any appreciable addition of nitrosyl compounds to the olefin occurs in our conditions, but hope to settle the point in a current investigation of olefinic additions.

subsequent reaction of *tert.*-butyl nitrite with bromide ion to give nitrosyl bromide. Up to this point, all the runs were accurately represented by the first-order rate law. A summary of the rate constants is given in Table 5.

TABLE 5. *First-order rate constants (k_1 in sec.$^{-1}$) of decomposition of* tert.*-butyl bromide in the presence of tetraethyl- or tetramethyl-ammonium nitrite in nitromethane: variation with salt concentration and with temperature.*

Run	Temp.	$[Bu^tBr]_0$	Salt	$[Salt]_0$	10^5k_1
31A	25·0°	0·0200	NEt_4NO_2	0·0048	0·391
16A	,,	0·0202	,,	0·0916	0·519
17A	,,	0·0201	,,	0·0306	0·556
63	25·1	0·0155	NMe_4NO_2	0·0323	0·557
62	45·0	0·0155	,,	,,	5·24
64	62·6	0·0155	,,	,,	29·0

From the first-order character of the rates, and the fact that the rate constants rise only slightly during a proportionately large increase in the reagent concentration, it can be concluded that the observed reactions are unimolecular, having a common rate-governing step, the ionisation of the alkyl bromide.

The temperature dependence of the rate is represented by the equation $k_1 = Be^{-E/RT}$ sec.$^{-1}$ with the substitutions $\log_{10} B = 9{\cdot}86$ and $E = 20{\cdot}6$ kcal./mole.

The slow increase in the rate of the total nitrite-ion reaction with increasing concentration of the saline reagent, *viz.*, about 40% of rate change for a 6-fold concentration change, is roughly the same as that found both for the elimination induced by chloride ions, and for the total chloride-ion reactions; and it is of the same order of magnitude as that observed for the bromide-ion exchange, although the larger errors inherent in the radioactive measurements, and also the temperature difference, preclude close comparison with this case. It seems clear therefore that the effect for the nitrite-ion reactions should be classified as a salt effect, just as for the other reactions.

The demonstration here given of a unimolecular mechanism for the reaction of an alkyl halide with nitrite ions is taken from a wider series of investigations by one of us (Y. P.), which show that both bimolecular and unimolecular substitutions (S_N2 and S_N1) as well as catalysed forms, such as the silver-ion mechanism (S_N1–Ag), can occur with this substituting agent, according to the alkyl halide, the solvent, and the catalyst. The question of the bearing of the mechanism of substitution on the nature of the products, whether they are nitro-compounds or alkyl nitrites, will be discussed in a forthcoming publication. Parallel investigations of the relation of mechanism to products in the reactions of alkyl halides with thiocyanate and with cyanide ions have shown that similar considerations are fundamental in these cases also.

(4) *Comparison of the Rates of Reaction of* tert.*-Butyl Bromide with Various Reagents.*—This comparison was the original object of the present work. In the results of this and the preceding paper, rate data can be found for seven reagents. Table 6 assembles the directly determined rates at 25·0° for the lowest concentration of each reagent used in measurements at this temperature. Though the concentrations are not ideally low, and are not even equal, all the rates are within 15% of the common value $0{\cdot}45 \times 10^{-5}$ sec.$^{-1}$. If we use the rate data for higher reagent concentration to effect an asymptotically linear extrapolation to zero concentration, all the extrapolated rates are within 5% of the common value $0{\cdot}38 \times 10^{-5}$ sec.$^{-1}$. This is strong evidence that, whatever may be the stoicheiometry of the reactions, all of them, substitutions and eliminations, are rate-controlled by a common process in which the reagent plays no part. Bearing in mind also the first-order forms of the reactions, we conclude that the mechanism throughout is unimolecular, the common slow step being the ionisation of the alkyl halide.

This demonstration of the essential identity of the rates of reaction of *tert.*-butyl bromide with different reagents at 25·0° is extended to other temperatures in three cases by determination of the Arrhenius parameters, which are compared in Table 7.

As far as our experiments show, the rates of the reactions with tertiary amines are independent of the amine concentration. The rates of the reactions with the other

reagents vary with the concentration of reagent. For the three hydroxylic reagents the variation is discussed in the preceding paper. It remains to discuss rate variation with the concentration of the three anionic reagents. We have provisionally concluded, by the exclusion of other alternatives (Section 2), that these rate variations arise from long-range interactions of the general nature of salt effects. However, the physical mechanism

TABLE 6. *Rate constants (k_1 in sec.$^{-1}$) of reactions of* tert.*-butyl bromide in nitromethane at 25·0°.*

Reagent	Concn. of reag. (*c*)	Obs. 10^5k_1 (*c*)	Extrap. 10^5k_1 (*c*)	Stoicheiometric reactions
C_5H_5N	0·02	0·39	0·39	*E*1
H_2O	0·035	0·43	0·40	Mainly S_N1
EtOH	0·11	0·45	0·40	Mainly S_N1
PhOH	0·06	0·52	0·40	Mainly S_N1
Br^-	0·025	0·45	(0·41) *	S_N1 + a little *E*1
Cl^-	0·01	0·45	0·36	*E*1 + a little S_N1
,,	0·005	0·40	0·37	*E*1 only
NO_2^-	0·005	0·39	0·36	S_N1 (two products) + *E*1

* Estimate based on results obtained at a higher temperature.

TABLE 7. *Parameters of the equation $k_1 = Be^{-E/RT}$ sec.$^{-1}$ for reactions of* tert.*-butyl bromide in nitromethane.*

Reagent	Temp. range	[Reagent]	$\log_{10} B$	*E* (kcal./mole)
H_2O	0—40°	0·125	9·8	20·6
Br^-	22—50	0·023	9·8	20·6
NO_2^-	25—63	0·032	9·9	20·6

is not fully clear, because, although the ionic character of these reagents must be an important factor, the curves of rate against concentration do not steepen exponentially at higher concentrations, as is required for salt effects on unimolecular reactions by the simple theory which treats the ions as point charges (*J.*, 1940, 893). Possibly the deviations indicate, in addition to long-range effects of ionic strength, an appreciable incursion of medium-range interactions, either of a non-specific type depending on mutual interference between the outer solvation layers of the transition state of ionisation and of the reagent ions, or of the more specific type recently considered in connexion with certain unimolecular reactions in sulphur dioxide (*J.*, 1954, 634).

EXPERIMENTAL

Materials.—The methods of preparation or purification of the materials used are standard, or have been described in other papers from this laboratory, except for tetramethyl- and tetraethyl-ammonium nitrite, which were made both from the tetra-alkylammonium iodide and silver nitrite in acetonitrile, and from the tetra-alkylammonium sulphate, prepared through the hydroxide, and barium nitrite in dry methyl alcohol. In either case, the filtered solution was evaporated to dryness at room temperature, and the nitrite, which formed pale yellow crystals, was purified by crystallisation from acetonitrile–diethyl ether, and dried at 60° in a good vacuum. For tetramethylammonium nitrite, made by the " silver " method, found, NO_2^- = 38·15; and, made by the " barium " method, found, NO_2^- = 38·2; calc., 38·3%. For tetraethylammonium nitrite, made by the barium method, found, NO_2^- = 26·05; calc., 26·1%.

Reaction of tert.*-Butyl Bromide with Tetraethylammonium Bromide in Nitromethane.*—Radioactive ammonium bromide, supplied by the Atomic Energy Research Establishment, Harwell, was evaporated almost to dryness with an equivalent of tetraethylammonium hydroxide, and the product was then finally dried in a vacuum over phosphoric oxide at the temperature of boiling chloroform. The filtered solution of the residue in nitromethane was standardised by Volhard's method.

Known volumes of solutions of *tert.*-butyl bromide and of tetraethylammonium radiobromide in nitromethane were mixed in small tubes, which were sealed and immersed in the thermostat. After suitable intervals, tubes were removed and chilled, and the solvent and organic bromide were rapidly evaporated under reduced pressure. The remaining tetraethylammonium bromide was dissolved in water, and its radioactivity was measured, employing the type of counter usual for liquid samples and standard scaling equipment. Each sample was counted at least twice. From the decay curves, which corresponded to within experimental

error, with those expected for ^{82}Br as the only radioactive species, values were read to give counts for each sample at the same arbitrary time. The bromide content of each sample was also determined, and thus the activities, as measured, were corrected to give specific activities, referring in each experiment to the same arbitrary concentration of bromide ion.

If a and b are respectively the concentrations of alkyl bromide and tetraethylammonium bromide, and if C and $C - X$ are respectively the specific activities of the initial solution of tetraethylammonium bromide, and of a solution of the salt recovered from a reaction stopped after a time t, then the first-order constant is given by the equation (cf. le Roux and Sugden, *J.*, 1939, 1279),

$$k_1 = \frac{2{\cdot}303b}{(a+b)t} \log_{10} \left\{1 - \frac{X}{C}\left(1 + \frac{b}{a}\right)\right\}^{-1}$$

This formula is valid, and was used, when no appreciable exchange occurred during the time taken by the reaction mixtures to reach the temperature of the thermostat, as was true for all but the highest of the temperatures employed. When it was not true, then specific activities, X_1 and X_2 were measured at two times, t_1 and t_2, after the experimental temperature had been attained, and accordingly the equation was used in its difference form :

$$k_1 = \frac{2{\cdot}303b}{(a+b)(t_2 - t_1)} \log_{10} \left[\left\{1 - \frac{X_1}{C}\left(1 + \frac{b}{a}\right)\right\}\left\{1 - \frac{X_2}{C}\left(1 + \frac{b}{a}\right)\right\}^{-1}\right]$$

The results are in Table 1.

Reaction of tert.*-Butyl Bromide with Tetraethylammonium Chloride in Nitromethane.*—For the determination of halide ions by potentiometric titration with silver nitrate, a calomel half-cell was connected by a potassium nitrate bridge to the solution to be titrated, a silver wire acting as the second electrode. The method of operation was based on the work of Clark (*J.*, 1926, 749), who showed that bromide and chloride could be individually estimated in a mixture, if 5% of barium nitrate was present in the solution. Equivalence points were located following the recommendations of Flood and Slatten (*Z. analyt. Chem.*, 1938, **115**, 30). Two methods were used for the preparation for titration of samples withdrawn from the kinetic runs. In the first (the " extraction " method), the sample (10 c.c.) was delivered into carbon tetrachloride (60 c.c.) at −10°, and this solution was shaken three times with 20 c.c. of ice-cold water. Barium nitrate (3 g.) was added to the total aqueous extract. In the second (the " evaporation ") method, the sample was run into a flask immersed in a freezing mixture, and evaporated with the aid of a high-capacity pump; and the residue was dissolved in 5% aqueous barium nitrate. For the determination of acid, the sample (10 c.c.) was run into dry acetone

TABLE 8. *Reaction of* tert.*-butyl bromide with tetraethylammonium chloride in nitromethane at 25·0° : illustrative kinetic runs.*

Run 86. Initially, $[Bu^tBr] = 0{\cdot}0202$M; $[NEt_4Cl] = 0{\cdot}0204$M; $[Br^-]$, as given by evaporation method, is in c.c. of 0·01N-$AgNO_3$ per 10 c.c. sample.

$k_1 = (2{\cdot}303/t) \log_{10} \{0{\cdot}202/(0{\cdot}202 - x)\}$ sec.$^{-1}$.

t (min.)	$[Br^-]$ (c.c.)	10^5k_1
30	0·20	0·563
60	0·40	0·557
90	0·65	0·610
120	0·80	0·569
150	1·00	0·565
180	1·10	0·517
240	1·60	0·574
330	2·00	0·526
	Mean	0·56

Run 8*A*. Initially, $[Bu^tBr] = 0{\cdot}0201$M; $[NEt_4Cl] = 0{\cdot}0111$M; $[H^+]$ is expressed in c.c. of 0·0543N-NaOMe per 10 c.c. sample.

$k_1 = (2{\cdot}303/t) \log_{10} \{0{\cdot}0201/(0{\cdot}0201 - x)\}$ sec.$^{-1}$.

t (min.)	$[H^+]$ (c.c.)	10^5k_1
60	0·61	0·454
90	0·90	0·456
120	1·15	0·438
150	1·50	0·461
180	1·68	0·431
240	2·23	0·432
	Mean	0·45

(70 c.c.) at −30°, and titrated with standard sodium methoxide, with lacmoid as indicator. For the determination of olefin, the sample (10 c.c.) was added to dry methyl alcohol (70 c.c.) at −30°, and, after addition of excess of methyl-alcoholic bromine, solid potassium iodide was introduced, and the liberated iodine was titrated with thiosulphate. Table 8 records two runs in illustration of these kinetic measurements.

Reaction of tert.*-Butyl Bromide with Tetramethyl- or Tetraethyl-ammonium Nitrite in Nitromethane.*—These reactions were followed by determination of the liberated bromide ion by

potentiometric titration with silver nitrate in 1% aqueous sulphuric acid. Samples withdrawn from the kinetic runs were prepared for titration by the " extraction method " described in the preceding paragraph. An illustrative run is recorded in Table 9.

TABLE 9. *Reaction of* tert.*-butyl bromide with tetramethylammonium nitrite in nitromethane at 62·6° : illustrative kinetic run.*

Run 64. Initially, [Bu^{t}Br] = 0·0155M; NMe_4NO_2 = 0·0323M. Sealed tube technique used. [Br^-] expressed in c.c. of 0·01N-$AgNO_3$ per sample of 5·48 c.c. [Br^-]$_{corr.}$ is the value of[Br^-] corrected for reaction before the first measurement at time t = 0, and for the separately determined, small amount of hydrolysis, which occurs during preparation of the samples for titration. The rate constant is calculated from $k_1 = (2{\cdot}303/t) \log_{10} \{7{\cdot}6/(7{\cdot}6 - [Br^-]_{corr.}\}$ with t in sec. and [Br^-]$_{corr.}$ in the above units.

t (sec.)	[Br^-]$_{corr.}$	10^5k_1	t (sec.)	[Br^-]$_{corr.}$	10^5k_1
300	0·65	29·8	840	1·65	29·1
400	0·85	29·7	900	1·75	29·1
420	0·85	28·2	1800	3·03	28·3
460	0·95	29·0	1920	3·23	28·6
600	1·20	28·7	2100	3·43	28·8
600	1·23	29·4			
				Mean	29·0

Incidentally to a larger programme, preliminary work on the chloride-ion reaction, which disclosed the difficulties later overcome, was done by Dr. Paul J. C. Fierens, now of the University of Brussels. We also received material help in the present experiments from Messrs. P. J. Collins and A. Spiers.

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Mechanism of Substitution at a Saturated Carbon Atom. Part XLI. Unimolecular Racemisation of* 1*-Mesitylethyl Chloride in Acetone.*

By J. C. CHARLTON and E. D. HUGHES.

[Reprint Order No. 5299.]

Optically active 1-mesitylethyl chloride undergoes racemisation in anhydrous acetone at a rate which has the kinetic characteristics associated with unimolecular reactions. This is the first evidence that such reactions can be realised in that solvent.

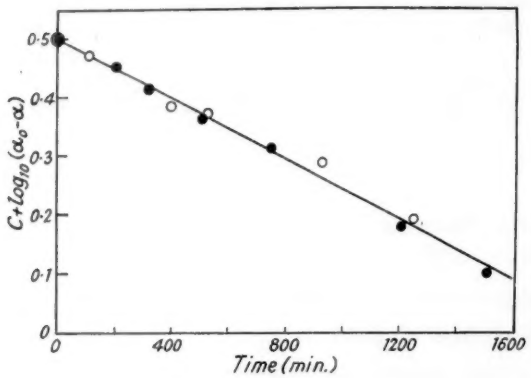
WHEN searching for evidence of the occurrence of unimolecular non-solvolytic reactions in polar aprotic solvents, we were not confident that we could encounter it in a solvent so far down the polar series as acetone. However, we have observed that optically active 1-mesitylethyl chloride racemises spontaneously in anhydrous acetone at a rate which has the kinetic characteristics of a unimolecular reaction. By introducing a mesityl group close to the site of reaction, we favour unimolecular substitution; but, as will be illustrated in a later paper, certain bimolecular substitutions, although somewhat slow, can be realised in this system. Again, by the use of a chloride, rather than a bromide or iodide, we offer bimolecular competition only by the least nucleophilic reagent-anion among the three halogens. The observations to be described depend on the assistance given to the unimolecular process by both the factors indicated.

Certain kinetic complications have to be dealt with. In the absence of any added substance, the spontaneous racemisation of 1-mesitylethyl chloride approximately follows a first-order law for nearly one-quarter of its course, and then becomes markedly autocatalytic. We ascribe the autocatalysis to a concomitant elimination of hydrogen chloride, the evidence being that it can be detected, and that added hydrogen chloride strongly accelerates the racemisation, almost completely cutting out the autocatalysis.

* Part XL, preceding paper.

Added neutral salts, such as lithium perchlorate, have a much smaller, but still considerable, accelerating influence on the first-order racemisation. They seem to have less influence on the autocatalytic process, with the result that they reduce the extent of this disturbance, and enable good rate coefficients to be obtained from a larger proportion, often one-half or more, of the total reaction. A large salt effect would be expected if the racemisation depends on a rate-controlling ionisation in anhydrous acetone. And though, for the convenience of the delay of autocatalysis, we used larger salt concentrations (up to 0·4M) than would justify an electrostatic calculation of the resulting kinetic effects (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979), it does appear that, up to about 0·2M-salt, the observed accelerations are of the order of those which could be calculated on the reasonable assumption that the ionic-strength constant σ for mesitylethyl chloride in acetone (which measures the polarity of the transition state of the ionisation) is not very different from that of the nearest analogous case for which we know it, *viz.*, for *pp'*-dimethylbenzylhydryl chloride in aqueous acetone (*loc. cit.*).

The crucial test of mechanism is, then, to keep the salt concentration constant, but to replace the inert salt, lithium perchlorate, by the conceivably active salt, lithium chloride. If the racemisation were bimolecular, depending, therefore, on adventitious chloride ion



Racemisation of 1-*mesitylethyl chloride in acetone at* 35° *in the presence of salts.*
● *With* 0·2M-$LiClO_4$.
○ *With* 0·2M-LiCl.

when none is added, then the introduction of lithium chloride should produce a great acceleration. In fact, as illustrated in the Figure for the concentration 0·2M of either salt, the first-order rates with added lithium perchlorate and with lithium chloride are almost the same. We conclude that the racemisation is essentially unimolecular, its velocity being dependent on a rate-determining fission of the carbon–halogen bond.

A selection of first-order rate coefficients, taken, where necessary, from the initial parts of the racemisations, are given in the Table, which illustrates, *inter alia*, the large

First-order rate coefficients (k_1 *in sec.*$^{-1}$) *of racemisation of* 1-*mesitylethyl chloride* (RCl) *in acetone.*

Run no.	[RCl]	[$LiClO_4$]	[LiCl]	[HCl]	10^5k_1	Run no.	[RCl]	[$LiClO_4$]	[LiCl]	[HCl]	10^5k_1
		At 35·0°						*At* 44·0°			
35	0·26	None	None	None	~0·05	167	0·23	None	None	None	0·11
37	0·27	0·20	,,	,,	1·03	164	0·16	0·20	,,	,,	1·9
38	0·26	None	0·20	,,	0·96	165	0·18	0·40	,,	,,	4·5
						168	0·054	0·20	,,	0·13	13

specific effect of hydrogen chloride. This cannot be due to its chloride ion, and must therefore be ascribed either to the molecule itself, or to its hydrogen ion. We interpret the effect as an electrophilic catalysis, dependent on hydrogen-bonding, of the ionisation of the alkyl halide, as illustrated for other reactions in the first of these three papers.

Comparison with the kinetics and rates of other reactions suggests that the margin of

rate, on which depends our ability to find unimolecular racemisation in the presence of, say, 0·2M-chloride ion, is narrow. It will appear from results to be published later that substitution by iodide ion in 1-mesitylethyl chloride is predominantly bimolecular, and that at 0·2M-salt concentration, its rate is of order 10^1 times greater than the rate of racemisation. From this, and the known rates of substitution by chloride and iodide ions in simple alkyl halides, we may infer that the rate of bimolecular racemisation in the presence of 0·2M-chloride ion is unlikely to be much smaller than 10^1 times less than the observed unimolecular rate. Another such comparison can be based, first, on results, later to be reported, which show that the effect of removing the three aromatic methyl substituents from 1-mesitylethyl chloride is to reduce the rates of both bimolecular and unimolecular substitutions, *viz.*, the iodide-ion substitution, and ethyl alcoholysis, but the latter by a factor of order 10^1 times larger; and secondly, on the evidence, from known substitution rates in simple alkyl halides, that, on going from an alkyl chloride to the corresponding bromide, both bimolecular and unimolecular racemisation rates should increase, the former by a factor not more than 10^1 times larger than the latter. Therefore the known result (Hughes, Juliusburger, Scott, Topley, and Weiss, *J.*, 1936, 1173), that the racemisation of 1-phenylethyl bromide in the presence of 0·2M-bromide ion in acetone is bimolecular, would be difficult to understand unless the rate of bimolecular racemisation of 1-mesitylethyl chloride in the presence of 0·2M-chloride ion is at least as large as 10^2 times smaller than the observed unimolecular rate.

The Experimental section describes a ketonic derivative of mesityl methyl ketone (of interest, because previous failures to prepare such derivatives have been ascribed to steric hindrance; Kadesch, *J. Amer. Chem. Soc.*, 1944, **66**, 1207), a new preparation of 1-mesitylethyl alcohol, an optical resolution (probably not complete) of this alcohol, and a preparation of optically active (not optically pure) 1-mesitylethyl chloride.

Experimental

Mesityl Methyl Ketone.—Mesitylene (200 g.), acetyl chloride (160 c.c.), and aluminium chloride (200 g.) in carbon disulphide (400 c.c.) yielded the ketone (210 g.), b. p. 128—130°/20 mm. (Dittrich and Meyer, *Annalen*, 1891, **264**, 138). A combined solution of the ketone (0·3 g.) in ethyl alcohol (10 c.c.) and of 2 : 4-dinitrophenylhydrazine (0·5 g.) in sulphuric acid (1 c.c.), after being boiled for 1·5 hr., deposited, on cooling, the 2 : 4-*dinitrophenylhydrazone*, which, after purification gave light yellow crystals (from aqueous ethyl alcohol), m. p. 141° (Found : C, 59·3; H, 5·6; N, 16·5. $C_{17}H_{18}O_4N_4$ requires C, 59·7; H, 5·3; N, 16·4%).

1-*Mesitylethyl Alcohol.*—The ketone (350 g.) was added gradually to lithium aluminium hydride (28 g.) in ether (1500 c.c.). After addition of dilute sulphuric acid, the ether solution was separated and evaporated, and the residue was poured into water; the alcohol solidified (338 g.). Crystallised from ether at −80°, it had m. p. 71—72° (in agreement with Klages and Allendorf, *Ber.*, 1898, **31**, 998). Its phenylurethane had m. p. 125°. The alcohol (82 g.), phthalic anhydride (74 g.), and pyridine (40 c.c.) were together heated on the steam-bath for 5 hr., cooled, mixed with acetone (100 c.c.), and poured on a mixture of ice (500 g.), concentrated hydrochloric acid (55 c.c.), and ligroin (200 c.c.); and the solidified *hydrogen phthalate* (127 g.) was collected and crystallised quickly from benzene–ligroin; its m. p. was then at first 90°, but during several days rose to 131—132°; slow crystallisation yielded large prisms, m. p. 134—135° (Found : C, 73·5; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·0; H, 6·5%). From this acid-ester (127 g.) and brucine (160 g.), the brucine salt was formed in boiling ethyl alcohol (1200 c.c.), collected from the hot suspension (86 g.), extracted with fresh hot solvent (360 c.c.), and then crystallised 5 times from ethyl alcohol, to yield a sample (25 g.) having $[\alpha]_D^{23}$ −8·7° (*c* 5 in $CHCl_3$). The free acid-ester, liberated from this salt, did not solidify, but had $[\alpha]_D^{23}$ −67° (*c* 5 in EtOH), and, on saponification for a few minutes with boiling 2N-sodium hydroxide (400 c.c.), gave a mesitylethyl alcohol, which separated as an oil and then rapidly solidified (3·4 g.). Crystallised from ligroin at −80°, it had $[\alpha]_D^{23}$ +45·8° (*c* 5 in EtOH). In a subsequent preparation the final rotation, measured in the same conditions, was raised to $[\alpha]_D^{17}$ +49·7°.

1-*Mesitylethyl Chloride.*—The optically active alcohol (1·0 g.) and thionyl chloride (0·6 c.c.) were allowed to react in boiling benzene (10 c.c.) for 10 min., and the solvent and excess of thionyl chloride were pumped off at room temperature. The 1-*mesitylethyl chloride* was then collected by short-path high-vacuum distillation, without application of heat, on a cold-finger

at −80°, and was subsequently run into an ampoule, which was sealed and kept at −80° until required. The chloride content was determined by electrometric titration in aqueous ethyl alcohol (Found: Cl, 19·5. $C_{11}H_{15}Cl$ requires Cl, 19·5%). The above-mentioned sample of 1-mesitylethyl alcohol, having $[\alpha]_D^{23}$ +45·8° in ethyl alcohol, gave a chloride which had $[\alpha]_D^{23}$ +60·4°, as measured on the pure liquid.

Kinetic Measurements.—The acetone was purified with the aid of potassium permanganate and dried finally with magnesium perchlorate. The purified and dried lithium salts were precipitated by filtering their acetone solutions into benzene, and were then again dried at 100° in a vacuum. The faster reactions were followed in a 10-cm. jacketed polarimeter tube, using sodium-D light. For the slower runs, the sealed tube technique was used in conjunction with polarimetric measurements. Concentrations were as given by weighing, except that of hydrogen chloride, which was passed in as gas, and determined by analysis. The details are here given of Run 168: [mesitylethyl chloride] = 0·054M, $[LiClO_4]$ = 0·0201M, [HCl] = 0·128M, k_1 in sec.$^{-1}$ (mean $10^5 k_1$ = 13·2):

t (min.)	α	Racn. (%)	10^5k_1	t (min.)	α	Racn. (%)	10^5k_1
0	0·90°	0·0	—	52	0·60°	33·8	13·7
12	0·83	9·2	13·4	62	0·55	38·9	13·5
17	0·79	12·2	12·5	72	0·51	43·3	13·1
22	0·75	16·7	13·8	82	0·47	47·8	13·2
32	0·70	22·2	13·1	92	0·43	51·7	13·2
42	0·66	26·7	12·4	207	0·18	80·0	13·0

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Titanium Tetrachloride as a Catalyst in the Friedel–Crafts Reaction. Part III. Alkylation.*

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Titanium tetrachloride has been successfully used as a catalyst for the alkylation of benzene, toluene, and anisole by, *e.g.*, tertiary alkyl chlorides, primary, secondary, and tertiary alcohols, and 2-methylbut-2-ene.

With the alkyl chlorides small proportions of the titanic halide sufficed to promote reaction, but with the alcohols at least an equivalent amount was required for the most satisfactory results.

With benzene, in addition to monosubstitution some disubstitution also occurred in some cases, the second group entering the *para*-position exclusively; with toluene and anisole *para*-substitution was the invariable rule.

Moreover, while *sec.*-butyl alcohol gave *sec.*-butyl derivatives *iso*butyl alcohol tended to yield *tert.*-butyl derivatives.

ALKYLATIONS with alkyl chlorides in the presence of titanic chloride appear to have been described only by Stadnikov and Kashtanov (*J. Russ. Phys. Chem. Soc.*, 1928, **60**, 1117; *Ber.*, 1928, **61**, 1389), who prepared in this way diphenylmethane and *m*- and *p*-dibenzylbenzene from benzene and benzyl chloride.

While titanium tetrachloride is not as active catalytically as aluminium chloride, certain advantages over the latter were noted: owing to its solubility in organic solvents reactions could be carried out in homogeneous media, and solvents such as carbon disulphide could be dispensed with. Also noteworthy was the absence of much polyalkylation; all disubstituted products were *para* only, and not mixed *para* and *meta* as frequently obtained with the aluminium halide.

* Part II, *J.*, 1952, 4106.

Early experiments with benzene showed that methyl and ethyl chloride did not react easily; however *tert.*-amyl and *tert.*-butyl chloride readily formed alkyl derivatives of benzene, toluene, and anisole. The reaction between *tert.*-butyl chloride and benzene yielded *p*-di-*tert.*-butylbenzene, accompanied by a small amount of the mono-*tert.*-butyl derivative; *tert.*-amyl chloride gave appreciable quantities of mono- as well as *p*-di-*tert.*-amylbenzene.

Somewhat discordant results are reported in the literature for the action of *tert.*-butyl chloride on toluene. Shoesmith and McGechen (*J.*, 1930, 2231) claimed that with aluminium or ferric chloride a mixture of *meta*- and *para*-substituted products resulted; on the other hand Baur (*Ber.*, 1891, **24**, 2833), Buu-Hoï and Cagniant (*Bull. Soc. chim.*, 1942, **9**, 887), and Larner and Peters (*J.*, 1952, 680) found that with aluminium chloride the chief product was the *meta*-isomer, and the last-named authors, and Bialobrzeski (*Ber.*, 1897, **30**, 1773), obtained *para*-substitution only with ferric chloride. Buu-Hoï and Cagniant explained Shoesmith and McGechen's results as being due to the use of concentrated sulphuric acid for isomer separation; this induced the reversible isomerisation *m-tert.*- $\rightleftharpoons$ *p-tert.*-butyltoluene, yielding an equilibrium mixture of the two.

In our experiments the proportion of catalyst used had no pronounced effect on yields in alkylations with *tert.*-butyl or *tert.*-amyl chloride. The sole product isolated in each case was the *para*-compound. We found that the *tert.*-butyltoluene was most readily oxidised to *p-tert.*-butylbenzoic acid with dichromate and sulphuric acid. When anisole was treated with *tert.*-butyl and *tert.*-amyl chlorides *p-tert.*-derivatives only were produced, variation in temperature having very little effect on the yields obtained.

Alkylations with alcohols in the presence of titanic chloride have not been previously described in the literature. In our experiments satisfactory yields were usually obtained, and it was noted that while *iso*butyl alcohol gave tertiary-alkyl derivatives, *sec.*-butyl alcohol gave secondary derivatives. Moreover the ease of reaction was in the order tertiary > secondary > primary alcohol, though with methyl and ethyl alcohol reaction was usually slight. With *tert.*-butyl and *tert.*-amyl alcohol yields comparable to those given by the corresponding alkyl chlorides were obtained provided that the ratio of catalyst to alcohol was not less than 1 : 1 (raising this proportion had very little effect). This may be due, partly at least, to the loss of some titanium salt by reaction with the alcohol (cf. Cullinane *et al.*, *J. Appl. Chem.*, 1952, **2**, 250), *e.g.*, $TiCl_4 + 2ROH = TiCl_2(OR)_2 + 2HCl$.

With *tert.*-butyl alcohol and benzene both mono- and *p*-di-*tert.*-butylbenzene were formed, as with aluminium chloride (Huston, Fox, and Binder, *J. Org. Chem.*, 1938, **3**, 251; cf. Norris and Sturgis, *J. Amer. Chem. Soc.*, 1939, **61**, 1413). McKenna and Sowa (*ibid.*, 1937, **59**, 470) found that boron trifluoride gave in addition a small amount of the *o*-di-derivative.

tert.-Amyl alcohol yielded the mono- and *p*-di-*tert.*-derivative of benzene, low temperatures favouring formation of the latter. The former compound was obtained with aluminium chloride (Huston, Fox, and Binder, *loc. cit.*) and ferric chloride (Inatome *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 292). Both toluene and anisole reacted smoothly with *tert.*-butyl and *tert.*-amyl alcohol, variations in time or temperature having very little effect on the yields obtained. *p*-Alkyl derivatives were the sole products.

tert.-Amylene gave the same products as *tert.*-amyl alcohol with benzene, toluene, and anisole.

Rather high temperatures were needed to ensure the best yields in the reaction between *sec.*-butyl alcohol and benzene. No isomerization of the *sec.*-butyl group was detected, in agreement with the results obtained with aluminium chloride (Huston and Hsieh, *ibid.*, 1936, **58**, 439) and boron trifluoride (McKenna and Sowa, *loc. cit.*), the sole product being *sec.*-butylbenzene. Similarly no isomerization took place with toluene, and as with aluminium chloride (Tsukervanik and Tokareva, *J. Gen. Chem. Russia*, 1935, **5**, 764) *p-sec.*-butyltoluene was obtained.

Benzene and *iso*propyl alcohol reacted to give cumene, as with aluminium chloride (Huston and Hseih, *loc. cit.*; Tsukervanik and Taveeva, *Zhur. Obshchey Khim.*, 1952, **22**, 966); boron trifluoride yielded mono- and di-*iso*propylbenzene (McKenna and Sowa,

loc. cit.). Toluene gave *p*-cymene only, also obtained by Tsukervanik and Tokareva (*loc. cit.*) with aluminium chloride, though Pajeau (*Bull. Soc. chim.*, 1948, 59) isolated both *m*- and *p*-cymene with the latter catalyst, whereas with sulphuric acid or ferric chloride all three *iso*propyltoluenes resulted.

The last-named author found that the action of aluminium chloride on *iso*propyl alcohol and anisole gave only *p-iso*propylanisole, but with titanium tetrachloride we obtained in addition *p-iso*propylphenol, formed by scission of the ether linkage.

No marked alkylation of benzene occurred with *iso*butyl alcohol; with toluene, isomerization to *p-tert.*-butyltoluene took place; Pajeau, using aluminium chloride, isolated both the *m*- and the *p-tert.*-butyl derivative. Anisole formed the *p*-tert.-butyl ether which was also given with aluminium chloride (Pajeau); in addition we obtained *p-tert.*-butylphenol. Somewhat high temperatures were needed in these experiments.

Experimental

A large number of experiments were carried out under varying conditions; some typical examples are described below and further results are given in the Table. The yields, while only approximate, were confirmed by repetition in many cases; all are based on the alkylating agent.

All materials were purified before use and precautions taken to exclude moisture.

Alkylation with Alkyl Chlorides.—The usual procedure consisted in adding the catalyst to the other reactants in a vessel fitted with a reflux condenser, and as heat was normally evolved cooling was applied during the addition, with continuous agitation. At the end of each alkylation the cooled product, which usually contained a little tar, was decomposed cautiously with dilute hydrochloric acid, and the organic layer separated, washed successively with dilute hydrochloric acid and water, and dried ($CaCl_2$). The products formed were fractionally distilled through a column.

Action of tert.-*Butyl Chloride on Benzene.*—Fractionation of the product gave a portion, b. p. 165—168°, consisting almost entirely of *tert.*-butylbenzene, b. p. 167° (cf. Norris and Sturgis, *loc. cit.*; McKenna and Sowa, *loc. cit.*; Tsukervanik, *J. Gen. Chem. Russia*, 1935, **5**, 117), which was identified by the following derivatives: (*a*) *p*-acetamido-, m. p. 171—172° (Ipatieff and Schmerling, *J. Amer. Chem. Soc.*, 1937, **59**, 1050; Potts and Carpenter, *ibid.*, 1939, **61**, 663; Malherbe, *Ber.*, 1919, **52**, 322); (*b*) 2 : 4-dinitro-, m. p. 61—62° (Baur, *Ber.*, 1894, **27**, 1710; Malherbe, *loc. cit.*); (*c*) the *p*-sulphonamide, m. p. 136° (Huntress and Autenrieth, *J. Amer. Chem. Soc.*, 1941, **63**, 3446). A higher fraction, *p*-di-*tert.*-butylbenzene, b. p. 230—235°, solidified on cooling, then having m. p. and mixed m. p. 77° (cf. McKenna and Sowa, *loc. cit.*).

Action of tert.-*Amyl Chloride on Benzene.*—Two fractions resulted. One, b. p. 189—192°, composed of *tert.*-amylbenzene, b. p. 191° (cf. Ipatieff and Schmerling, *loc. cit.*), was identified by the following derivatives: the *p*-sulphonamide, m. p. 85—86° (Legge, *J. Amer. Chem. Soc.*, 1947, **69**, 2079; Huntress and Autenrieth, *loc. cit.*); *p*-acetamido-, m. p. 138° (Anschütz and Beckerhoff, *Annalen*, 1903, **327**, 22; Ipatieff and Schmerling, *loc. cit.*; Legge, *loc. cit.*); the second fraction, b. p. 262—266°, was almost entirely *p*-di-*tert.*-amylbenzene, b. p. 264° (cf. Simons and Archer, *J. Amer. Chem. Soc.*, 1938, **60**, 2952). This fraction (4 g.) was heated with chromic oxide (14 g.), water (60 c.c.), and concentrated sulphuric acid (66 c.c.) at 70°. When the reaction had subsided more chromic oxide (32 g.) was added gradually and the mixture was further heated at 100° for 30 min., then poured into water; terephthalic acid (1·5 g.) (dimethyl ester, m. p. 139—140°) was precipitated.

Action of tert.-*Butyl Chloride on Toluene.*—The product, b. p. 188—191°, consisted almost exclusively of *p-tert.*-butyltoluene, b. p. 191° (cf. Larner and Peters, *loc. cit.*), and was characterized by the following derivatives: 2-benzamido-, m. p. 142° (Battegay and Haeffely, *Bull. Soc. chim.*, 1924, **35**, 981); 2 : 6-dinitro-, m. p. 94—95° (Brady and Lahiri, *J.*, 1934, 1954); *sulphonamide*, colourless plates, m. p. 138—140° (Found: C, 58·6; H, 7·8; N, 6·1; S, 14·0. $C_{11}H_{17}O_2NS$ requires C, 58·1; H, 7·5; N, 6·2; S, 14·1%).

p-tert.-*Butylbenzoic Acid.*—Larner and Peters failed to oxidize *p-tert.*-butyltoluene by Bialobrzeski's chromic acid–acetic acid method, but secured a 35% yield of the acid by oxidation with potassium permanganate in aqueous pyridine. We obtained a 55% yield by heating the hydrocarbon (5 g.) with sodium dichromate (20 g.), water (90 c.c.), and concentrated sulphuric acid (75 c.c.) gradually to 45°; the reaction tended to become violent, but the temperature was not allowed to exceed 50°. After this reaction had subsided more sodium dichromate (25 g.) was added in small portions, the temperature being still kept at 50°, and the mixture was then

Alkylations (quantities in moles; the heading Cpd. refers to the amount of the aromatic reactant. When two values are given for the yield, the first refers to the mono- and the second to the di-alkyl product; single figures refer to monoalkyl derivatives).

$TiCl_4$	Cpd.	Temp.	Time (hr.)	Yield (%)	Note
	Benzene and tert.-*butyl chloride.*				
0·1	0·28	10°	3	9 + 69	—
0·1	0·28	10	6	4 + 84	1
	Benzene and tert.-*amyl chloride.*				
0·1	0·28	60	3	14 + 57	2
0·1	0·28	20	18	27 + 52	—
	Toluene and tert.-*butyl chloride.*				
0·025 or 0·05	0·24	10	1	73	—
0·1	0·24	10	1 or 3	77	—
	Toluene and tert.-*amyl chloride.*				
0·05	0·24	20	3	61	3
0·1	0·24	20	1	58	4
0·1	0·24	40	3	69	—
	Anisole and tert.-*butyl chloride.*				
0·1	0·2	10	0·5	64	—
0·1	0·2	0 or 10	1	71	5
	Anisole and tert.-*amyl chloride.*				
0·1	0·2	20 or 60	1	67	6
	Benzene and tert.-*butyl alcohol.*				
0·2	0·55	60	1	74 + 4	7
0·2	0·55	60	2	71 + 8	8
0·2	0·55	80	1	66 + 7	—
0·2	0·55	40	3	36 + 46	9
	Benzene and tert.-*amyl alcohol.*				
0·2 or 0·1	0·55	60	1	74	—
0·2	0·55	80	1	60 + 11	10
0·2	0·55	18	18	41 + 28	11
	Toluene and tert.-*butyl alcohol.*				
0·2	0·47	10	3	74	12
0·2	0·47	25	6	74	—
0·1	0·47	10	3	74	13
	Toluene and tert.-*amyl alcohol.*				
0·2	0·47	18	3	64	14
0·2	0·47	18	6	70	15
0·2	0·47	40	3	68	—
	Anisole and tert.-*butyl alcohol.*				16
0·2	0·2	10	1	67	17
0·1	0·2	10	1	67	18
	Anisole and tert.-*amyl alcohol.*				16
0·2	0·2	20	0·25	61	19
0·2	0·2	0	1	57	20
0·1	0·2	20	1	61	—
	Benzene and sec.-*butyl alcohol.*				
0·1 or 0·2	0·55	B. p.	6	61	—
	Benzene and iso*propyl alcohol.*				
0·1 or 0·2	0·55	B. p.	6	61	—
	Toluene and sec.-*butyl alcohol.*				
0·1	0·24	100	3	68	21
0·2	0·47	60	4·5 or 3	74	—
0·2	0·24	60	3	66	—
	Toluene and iso*propyl alcohol.*				
0·2	0·47	100	3	68	22
0·1	0·47	100	0·5	59	23
	Anisole and iso*propyl alcohol.*				24
0·1 or 0·2	0·2	100	3	44 (14)	—
0·2	0·2	140	1	53 (22)	—
	Toluene and iso*butyl alcohol.*				
0·2	0·47	B. p.	6	62	25
	Anisole and iso*butyl alcohol.*				
0·1	0·2	160	3	75	26
	Benzene and 2-methylbut-2-ene.				
0·1	0·55	60	9	13 + 42	27
0·1	0·55	80	6	40	—
	Toluene and 2-methylbut-2-ene.				
0·1	0·24	20	1	18	28
0·05	0·24	20	3	16	29
	Anisole and 2-methylbut-2-ene.				30
0·1	0·2	0	1	61	31
0·1	0·2	20	0·25 or 0·5	67	

Notes: With other conditions throughout as stated, further yields obtained were as follows: (1) With 0·55 mole of benzene 19 and 66%. (2) After 6 hr. 29 and 56%. With 0·55 mole of benzene 23 and 28%. (3) With 0·1 or 0·2 mole of titanic chloride 68%. (4) After 6 or 13 hr. 70%. (5) When anisole was added to the other ingredients at 10° 64%. (6) With 0·05 or 0·2 mole of titanic chloride at 20°, the yield was the same. (7) With 0·1 mole of titanium tetrachloride 71 + 8%, and with 0·05 mole 49 + 29%. (8) With 0·2 mole of benzene 63 + 16%. (9) With 0·2 mole of benzene 20 + 66%. (10) After 3 hr. at 60° 69 + 12%. (11) After 48 hr. 47 + 33%. (12) After 6 hr. 74, 48 hr. 77%. (13) With 0·05 mole of titanium tetrachloride 35%. (14) With 0·3 mole of titanium tetrachloride 64%, with 0·1 mole 57%. (15) After 18 hr. same yield. (16) The catalyst was added to the alcohol and anisole, mixed with carbon disulphide (30 c.c.). (17) After 2 hr. same yield; after 1 hr. at 40° 66%. (18) With 0·05 mole of catalyst 53%; with 0·3 mole 67%. (19) After 1 or 3 hr. same yield. (20) At 40° 61%. (21) At 80° same, at 60° 65%, at 40° 28%. (22) At 80° 62%, at 60° 61%, at 40° 57%, at 20° 19%. (23) After 1 hr. 61%, 3 hr. 67%. (24) Figures in parentheses give the yields of *p-iso*propylphenol. (25) After 3 hr. 11%, 9 hr. 55%. (26) At 140° 60%, 120° 19%, 100° or 50° no yield. The products contained in all cases about equal amounts of *p-tert.*-butylanisole and *p-tert.*-butylphenol. (27) After 6 hr. 13 + 31%, 3 hr. 23 + 8%. (28) After 3 hr. 33%, 6 hr. 30%. (29) With 0·2 mole of titanium tetrachloride 33%. (30) Yields are of *p-tert.*-amylanisole. (31) At 20° 67%, 40° 65%, 60° 67%.

heated at 100° for 15 min. The cooled product was poured into water, and the solid collected and extracted with dilute sodium hydroxide solution from which the acid was precipitated. Recrystallization from ligroin yielded colourless needles, m. p. 163—164°. Larner and Peters give m. p. 162—164°.

Action of tert.-*Amyl Chloride on Toluene.*—The product, b. p. 212—214°, was composed almost exclusively of *p-tert.*-amyltoluene (cf. Hennion and Kurtz, *J. Amer. Chem. Soc.*, 1943, **65**, 1001). Oxidation by the method used for di-*tert.*-amylbenzene gave terephthalic acid, and the *sulphonamide* crystallized from hot water in fine white needles, m. p. 113—114° (Found: C, 59·5; H, 7·8; N, 5·7; S, 13·5. $C_{12}H_{19}O_2NS$ requires C, 59·7; H, 7·9; N, 5·8; S, 13·3%).

4-tert.-*Amyl*-2-*benzamidotoluene.*—A mixture of nitric acid (*d* 1·42; 6 c.c.) and concentrated sulphuric acid (6 c.c.) was added gradually to *tert.*-amyltoluene (8 c.c.) at 15—20°, stirring being continued for a further 30 min. The product was poured into water, and the nitro-compound (6·7 g.) extracted with ether; it distilled at 125—130°/4 mm. Reduction followed by benzoylation yielded 4-tert.-*amyl*-2-*benzamidotoluene*, colourless plates (from alcohol), m. p. 122—123° (Found: C, 80·6; H, 8·0; N, 5·1. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2; N, 5·0%).

The methyl group in the above nitro-compound, dissolved in acetic anhydride and acetic acid, was oxidized with chromium trioxide to aldehyde diacetate. Hydrolysis of this product with hydrochloric acid yielded a compound which gave a strong positive Baeyer–Drewson indigo test (*Ber.*, 1883, **16**, 2205) for *o*-nitrobenzaldehydes.

4-tert.-*Amyl*-2 : 6-*dinitrotoluene.*—*p-tert.*-Amyltoluene (30 g.) in glacial acetic acid (30 c.c.) was cooled in ice-salt, and fuming nitric acid (*d* 1·5; 60 c.c.) and oleum (66 c.c.) containing 20% of free sulphur trioxide were added slowly below 5° with stirring. After being kept in the bath for a further 30 min., the mixture was heated at 40° for 3 hr. The cooled mixture was then poured on crushed ice, and the precipitated solid washed with aqueous sodium carbonate and water. Crystallization from alcohol afforded colourless crystals of 4-tert.-*amyl*-2 : 6-*dinitrotoluene*, m. p. 61—62° (Found: C, 57·7; H, 6·4; N, 10·9. $C_{12}H_{16}O_4N_2$ requires C, 57·1; H, 6·3; N, 11·1%).

3 : 5-*Dinitro*-p-*toluic Acid* (CO_2H = 1).—The above solid (3 g.) was boiled under reflux with fuming nitric acid (*d* 1·5; 75 c.c.) for 120 hr., then the product was poured into water. After a few days pale yellow needles appeared and a further quantity was obtained from the mother-liquor. Recrystallization from hot water afforded 3 : 5-dinitro-*p*-toluic acid (1·5 g.), m. p. 158—159°, also obtained by oxidation of 2 : 6-dinitro-*p*-cymene by Wheeler and Harris (*J. Amer. Chem. Soc.*, 1927, **49**, 494).

4-tert.-*Amyl*-2-*nitro*-6-*benzamidotoluene.*—The *tert.*-amyl-dinitrotoluene (5 g.) was reduced with ammonium sulphide (16% solution; 30 c.c.) in ethanol (50 c.c.); the *amine hydrochloride* (4·1 g.) crystallized from dilute hydrochloric acid in pale yellow needles, m. p. 220° (decomp.) (Found: *M*, by titration, 256·9. $C_{12}H_{19}O_2N_2Cl$ requires *M*, 258·5%). The *benzoyl* derivative formed colourless plates (from dilute alcohol), m. p. 135° (Found: C, 69·7; H, 6·6; N, 8·7. $C_{19}H_{22}O_3N_2$ requires C, 69·9; H, 6·7; N, 8·6%).

Action of tert.-*Butyl Chloride on Anisole.*—The product, b. p. 222—225° (mostly 222—223°), m. p. 19°, was *p-tert.*-butylanisole (cf. Olsen *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 2451). The 2 : 6-dinitro-derivative had m. p. 100° (Baur, *Ber.*, 1894, **27**, 1618).

Action of tert.-*Amyl Chloride on Anisole.*—*p-tert.*-Amylanisole, b. p. 239—240°, was the sole product. Fischer and Grützner (*Ber.*, 1893, **26**, 1648) give b. p. 240—241°; Kreysler (*Ber.*, 1885, **18**, 1711) gives 216—217°.

4-tert.-*Amyl*-2 : 6-*dinitroanisole.*—To the ether (2 g.) in glacial acetic acid (10 c.c.), cooled in ice, fuming nitric acid (*d* 1·5; 4 c.c.) in acetic acid (10 c.c.) was added dropwise, followed by concentrated sulphuric acid (4 c.c.) in the same solvent (5 c.c.). The product was then heated at 70° for 30 min., cooled, and poured on ice. The precipitated oil solidified slowly and after recrystallization from alcohol or dioxan gave yellow needles (1 g.), m. p. 38°. Anschütz and Rauff (*Annalen*, 1903, **327**, 213), who prepared the compound by methylation of the phenol, give m. p. 39°.

Alkylation with Alcohols.—Similar procedures were adopted to those used with alkyl chlorides. The products obtained by treatment of benzene, toluene, and anisole with *tert.*-amyl and *tert.*-butyl alcohol were isolated and identified by the methods already described, and the results are summarized in the Table.

Action of sec.-*Butyl Alcohol on Benzene.*—The fraction, b. p. 170—175°, was almost all *sec.*-butylbenzene, b. p. 173° (cf. Birch, Dean, Fidler, and Lowry, *J. Amer. Chem. Soc.*, 1949, **71**, 1362), which was identified by the *p*-acetamido-derivative, m. p. 123° (Harrison, Kenyon, and Shepherd, *J.*, 1926, 659). A small quantity of a higher-boiling fraction was also formed.

Action of sec.-*Butyl Alcohol on Toluene.*—The liquid, b. p. 192° (cf. Welsh and Hennion,

J. Amer. Chem. Soc., 1941, **63**, 2603), was *p-sec.*-butyltoluene, which was oxidized in the usual way to terephthalic acid. Its mononitro-derivative had b. p. 110—112°/3 mm. and the corresponding amine 100—102°. The benzoyl derivative, presumably 2-*benzamido*-4-sec.-*butyltoluene*, crystallized from alcohol in colourless needles, m. p. 139—140° (Found: C, 80·5; H, 8·0; N, 5·0. $C_{18}H_{21}ON$ requires C, 80·9; H, 7·9; N, 5·2%), depressed on admixture with 2-benzamido-4-*tert.*-butyltoluene.

Action of iso*Propyl Alcohol on Benzene.*—The product consisted of *iso*propylbenzene (cumene), b. p. 152° (cf. Potts and Carpenter, *loc. cit.*), together with a very small quantity of a higher-boiling fraction. The 4-sulphonamide, colourless plates, had m. p. 105—106° (cf. Huntress and Autenrieth, *loc. cit.*).

Action of iso*Propyl Alcohol on Toluene.*—The sole product was *p*-cymene, b. p. 177°, oxidized to terephthalic acid. 2-Methyl-5-*iso*propylacetanilide was prepared as colourless plates, m. p. 71° (cf. Goldschmidt, *Ber.*, 1893, **26**, 2086).

Action of iso*Propyl Alcohol on Anisole.*—The product collected at 200—230° was divided into alkali-soluble and alkali-insoluble portions. The former yielded *p-iso*propylphenol, b. p. 228° (cf. Huston *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 899) [benzoate, colourless plates, m. p. 71° (Tsukervanik and Nazarova, *J. Gen. Chem. Russia*, 1937, **7**, 623; Huston *et al.*, *loc. cit.*)]; the latter consisted almost completely of *p-iso*propylanisole, b. p. 213° (cf. Klages, *Ber.*, 1904, **37**, 3996).

Action of iso*Butyl Alcohol on Toluene.*—The product contained mainly *p-tert.*-butyltoluene, identified as described above. In addition some *p-iso*butyltoluene appeared to be present; oxidation gave some terephthalic acid, which was not formed from the former hydrocarbon under the same conditions.

Action of iso*Butyl Alcohol on Anisole.*—The resultant oil was shaken with 5% sodium hydroxide solution, and the insoluble portion taken up in ether, from which *p-tert.*-butylanisole, identified as already described, was obtained. The portion soluble in alkali was almost all *p-tert.*-butylphenol, white needles (from light petroleum), m. p. 97—98° [benzoate, m. p. 79—80° (cf. Henry and Sharp, *J.*, 1926, 2434)]. Nitration yielded bright yellow needles, m. p. 94°. Studer (*Ber.*, 1881, **14**, 1474) gives 93° and Henry and Sharp 97—98° as the m. p. of 4-*tert.*-butyl-2 : 6-dinitrophenol.

Treatment of *p-tert.*-butylphenol (1 g.) in acetic acid (8 c.c.) with nitric acid (*d* 1·42; 8 c.c.) at 0°, followed by heating to 80° for 1 hr., gave picric acid as sole product (cf. Jedlicka, *J. prakt. Chem.*, 1893, **48**, 98).

Action of 2-*Methylbut*-2-*ene on Benzene.*—*tert.*-Amyl and *p*-di-*tert.*-amylbenzene were formed and identified as described above.

Action of 2-*Methylbut*-2-*ene on Toluene.*—In addition to the main product, *p-tert.*-amyltoluene, b. p. 212—214°, a small amount of a product, b. p. 262—266°, which was probably *p*-di-*tert.*-amylbenzene (cf. Simons and Archer, *J. Amer. Chem. Soc.*, 1940, **62**, 1623) was isolated.

Action of 2-*Methylbut*-2-*ene on Anisole.*—*p-tert.*-Amylanisole was the chief product, but a small quantity of material, boiling above 250°, was also obtained.

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Some Alkyl and Acyl Derivatives of 2-Phenacylpyridine.

By A. H. Beckett and K. A. Kerridge.

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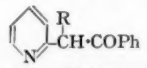
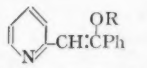
Alkylation of 2-phenacylpyridine with methyl, ethyl, propyl, and allyl halides gives *C*-alkyl derivatives exclusively, whereas 2-dimethylaminoethyl chloride causes *O*-alkylation. Acetylation gives the *O*-derivative but aroylation gives *C*-derivatives. Chemical and ultra-violet absorption data are presented in support of the structures assigned.

2-Phenacylpyridine, in the enolic form (II; R = H), reacts with cupric ions to form a cupric chelate compound (Goldberg, Barkley, and Levine, *J. Amer. Chem. Soc.*, 1951, **73**, 4301). Substitution of the methylene group of 2-phenacylpyridine has now been investigated in an attempt to vary the keto–enol ratio and the complexing properties of the system.

The sodio-derivative of 2-phenacylpyridine, prepared from 2-phenacylpyridine and powdered sodamide in toluene or by sodium methoxide in methanol, can react with acid anhydrides and alkyl and acyl halides to give the *C*- (I) or and the *O*-derivatives (II). Methyl iodide and benzyl chloride in toluene gave exclusively the *C*-alkyl compounds.

(I)   (II)

Solvents possessing higher dielectric constants than toluene were necessary for alkylations involving allyl, ethyl, and *n*-propyl bromide, and these halides also yielded *C*-derivatives (60—70% yield). Spectroscopic data indicated the absence of *O*-alkyl compounds even in the crude products from the above reactions. 2-Dimethylaminoethyl chloride in a solvent of equal parts of toluene and acetone gave the enol ether (78% yield) (II; R = $CH_2 \cdot CH_2 \cdot NMe_2$). From a consideration of hydrolysis experiments and ultra-violet absorption measurements, it was reported (Sperber, Fricano, and Papa, *ibid.*, 1950, **72**, 3068) that *C*-alkylation also occurred in this reaction, but we could not detect the presence of any amino-ketone. The alkylation of diphenylacetone with this halide also gave *O*-alkylation exclusively (Rinderknecht, *ibid.*, 1951, **73**, 5770) under conditions which yielded principally *C*-derivatives with non-basic alkyl halides. 2-Dimethylaminoethyl chloride is known (Knorr, *Ber.*, 1904, **37**, 3507; Simonella, Madrone, and Favini, *Gazzetta*, 1950, **80**, 129) to form cyclic 'onium cations in polar solvents; however, we obtained the *C*-benzyl compound of 2-phenacylpyridine when using benzyldimethylanilinium chloride.

The sodio-derivative of 2-phenacylpyridine in toluene with *p*-nitro- and *p*-chlorobenzoyl chloride gave the *C*-aroyl derivatives (70% yield), as did benzoic anhydride and 3 : 5-dinitrobenzoyl chloride in toluene–acetone, whereas acetic anhydride reacted readily with the sodio-derivative in toluene to give the *O*-derivative (75% yield). Attempted acylation of 2-phenacylpyridine by propionic and butyric anhydrides failed, as did attempted benzoylation, with benzoic anhydride, of 1-2′-pyridylbutan-2-one and 1-2′-pyridylpentan-2-one. The known ease of hydrolysis of 1 : 3-diarylpropane-1 : 3-diones by dilute alkalis (Bradley and Robinson, *J.*, 1926, 2356) may account for the recovery of starting material from these unsuccessful acylations.

Table 1. *Ultra-violet spectra, in ethanol, of 2-phenacylpyridine and its* C*-alkyl derivatives.*

R =	H	Me	Et	Pr^n	$CH_2 \cdot CH{:}CH_2$	CH_2Ph
$\lambda_{max.}$ (mμ)	244	247	247	247	247	247
$\varepsilon_{max.}$	10,700	13,800	14,000	12,300	13,000	15,400

Sperber *et al.* (*loc. cit.*) found that the ultra-violet absorption, in ethanol, of deoxybenzoin ($\lambda_{max.}$ 243 mμ), α-ethyldeoxybenzoin ($\lambda_{max.}$ 245 mμ), and 2-phenacylpyridine ($\lambda_{max.}$ 246 mμ) are similar. Table 1 indicates that the compounds listed are *C*-alkyl derivatives of 2-phenacylpyridine. The styryl derivatives of pyridine and benzene exhibit a high-intensity

absorption band in the region 295—310 mμ (Blout and Eager, *J. Amer. Chem. Soc.*, 1945, **67**, 1315). The structures of the *O*-derivatives of 2-phenacylpyridine (II; R = $-CH_2 \cdot CH_2 \cdot NMe_2$ or Ac) are indicated by the fact that their ultra-violet spectra resemble those of 2-stilbazole and stilbene (see Table 2).

TABLE 2. *Absorption spectra in ethanol.*

	2-Stilbazole *	Silbene *	(II; R = $CH_2 \cdot CH_2 \cdot NMe_2$)	(II; R = Ac)
$\lambda_{infl.}$ (mμ)	275—285	—	270—280	275—285
$\lambda_{max.}$	310	295	302—304	300—302
$\varepsilon_{max.}$	27,600	26,300	22,200	24,100

* Blout and Eager, *loc. cit.*

The ease of regeneration of 2-phenacylpyridine from its 2-dimethylaminoethyl derivative with 2N-sulphuric acid contrasts with the failure of the alkyl derivatives of Table 1 to hydrolyse under similar conditions and substantiates the structures assigned.

Evidence that aroylation gave *C*-derivatives was obtained by the preparation of 1-*p*-chlorophenyl-3-phenyl-2-2′-pyridylpropane-1 : 3-dione (I; R = $CO \cdot C_6H_4Cl$-*p*) by two independent methods. Aroylation of 2-phenacylpyridine with *p*-chlorobenzoyl chloride and of 2-*p*-chlorophenacylpyridine with benzoic anhydride yielded compounds which were identical in m. p. and spectroscopic data. Table 3 shows that the ultra-violet spectra of

TABLE 3. *Absorption spectra in ethanol* (λ *in* mμ) *of C-aroyl derivatives of 2-phenacylpyridine.*

(II; R = Bz)	$\lambda_{max.}$	251	310	370	$\lambda_{min.}$	—	280	332
	$\varepsilon_{max.}$	17,500	7,800	9,000	$\varepsilon_{min.}$	—	6,600	6900
(II; R = $CO \cdot C_6H_4Cl$-*p*)	$\lambda_{max.}$	255	310	370	$\lambda_{min.}$	230	283	326
	$\varepsilon_{max.}$	17,200	8,900	11,500	$\varepsilon_{min.}$	12,700	8,300	8500
(II; R = $CO \cdot C_6H_4 \cdot NO_2$-*p*)	$\lambda_{max.}$	255 *	—	370	$\lambda_{min.}$	—	—	325
	$\varepsilon_{max.}$	19,200	—	13,900	$\varepsilon_{min.}$	—	—	9000
[II; R = $CO \cdot C_6H_3 \cdot (NO_2)_2$-1 : 3 : 5]...	$\lambda_{max.}$	—	292	370	$\lambda_{min.}$	—	280	320
	$\varepsilon_{max.}$	—	10,000	12,600	$\varepsilon_{min.}$	—	10,200	7700

* Infl. 285 mμ (ε 15,000).

the other aroyl derivatives resemble that of the *p*-chlorophenacylpyridine derivative. These derivatives, in contrast to the other compounds reported, gave green colours in alcoholic ferric chloride. The picrate of 2-phenacylpyridine was obtained on attempting to prepare the picrates of these *C*-aroyl derivatives, in contrast to the reaction of *C*-alkyl and *O*-derivatives, which yield normal picrates.

The metal chelating properties of these compounds are being investigated in relation to their bacteriostatic activity.

EXPERIMENTAL

Ultra-violet absorption spectra were determined in absolute ethanol, with a Unicam S.P. 500 spectrophotometer, cell-path 1 cm. Microanalyses were by Mr. G. S. Crouch, School of Pharmacy, University of London.

Equiv. wts., except those of picrates, were determined by titration with 0·02N-perchloric acid in acetic acid; those of the picrates were determined by titration with 0·02N-sodium hydroxide in 1 : 1 ethanol–acetone with ethyl bis-2 : 4-dinitrophenylacetate as indicator.

Alkylation.—2-Phenacylpyridine with alkyl halides. The sodio-derivative of 2-phenacylpyridine, prepared by heating 2-phenacylpyridine (0·7 g., 0·004 mole) and sodamide (0·22 g.) in toluene (20 ml.) for 3 hr. at 80°, was heated with the alkyl halide (0·005 mole) at the temperature, and for the time, and in the solvent stated. The mixture was then cooled, aqueous ammonium chloride added, the organic layer separated, and the aqueous layer extracted with ether. The organic extracts were combined, washed with water, and dried ($MgSO_4$), and the solvent removed under reduced pressure to yield products which were purified by chromatography on alumina.

Products were recrystallised from ethanol unless otherwise stated.

Methyl iodide (40°; 3 hr.; toluene) gave α-2′-*pyridylpropiophenone* (I; R = Me) (64%), white rosettes, m. p. 64·5° (Found: C, 79·8; H, 6·2; N, 6·7%; equiv., 214. $C_{14}H_{13}ON$ requires C, 79·55; H, 6·15; N, 6·6%; equiv., 211).

Benzyl chloride (80°; 2 hr.; toluene) gave β-*phenyl*-α-2′-*pyridylpropiophenone* (I; R = CH_2Ph) (70%), white rosettes, m. p. 97—98° (Found: C, 83·8; H, 5·8; N, 4·8%; equiv., 289. $C_{20}H_{17}ON$ requires C, 83·6; H, 5·9; N, 4·9%; equiv., 287).

Benzyldimethylanilinium chloride (50°; 4 hr.; acetone–toluene) gave β-phenyl-α-2′-pyridylpropiophenone (66%), m. p. and mixed m. p. 97—98°.

Propyl bromide (50°; 12 hr.; acetone–toluene) gave α-2′-*pyridylvalerophenone* (I; R = Pr^n) (72%), a colourless oil, n_D^{20} 1·5640 (Found: C, 80·5; H, 7·5%; equiv., 244. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2%; equiv., 239). It gave a *picrate*, yellow prisms, m. p. 146—147° (Found: C, 56·8; H, 4·4; N, 12·3%; equiv., 470. $C_{22}H_{20}O_8N_4$ requires C, 56·4; H, 4·35; N, 12·0%; equiv., 468).

Allyl bromide (50°; 12 hr.; acetone–toluene) gave α-2′-*pyridylpent*-4-*enophenone* (I; R = CH_2·CH·CH_2) (75%), a colourless oil, n_D^{20} 1·5772 (Found: C, 81·6; H, 6·5%; equiv., 241. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4%; equiv., 237). It gave a *picrate*, orange prisms, m. p. 130—131° (Found: C, 56·4; H, 4·0; N, 11·8%; equiv., 467. $C_{22}H_{18}O_8N_4$ requires C, 56·6; H, 3·9; N, 12·0%; equiv., 466).

2-Dimethylaminoethyl chloride (50°; 12 hr.; acetone–toluene) gave α-2′-*dimethylaminoethoxy*-β-2′-*pyridylstyrene* (II; R = CH_2·CH_2·NMe_2) (78%), a colourless oil, n_D^{20} 1·5855 (Found: C, 75·4; H, 7·8; N, 10·0%; equiv., 137. $C_{17}H_{20}ON_2$ requires C, 76·1; H, 7·5; N, 10·4%; equiv., 134). Hydrolysis of the enol ether with 2N-sulphuric acid gave 2-phenacylpyridine. A *dipicrate* was prepared from the oil, and formed yellow prisms, m. p. 135° (decomp.) (Found: C, 48·5; H, 3·8; N, 15·2; equiv., 718. $C_{29}H_{26}O_{15}N_8$ requires C, 49·0; H, 3·9; N, 15·0%; equiv., 726).

Ethyl iodide (0·005 mole) and a solution of the sodio-derivative of 2-phenacylpyridine from 2-phenacylpyridine (0·75 g., 0·004 mole) and sodium (0·13 g.) in methanol (20 ml.) were heated at 50° for 0·5 hr. The methanol was distilled off and the mixture treated, as described in the general method, to yield α-2′-*pyridylbutyrophenone* (I; R = Et) (63%), white rosettes, m. p. 50° (Found: C, 79·6; H, 6·5; N, 6·5%; equiv., 227. $C_{15}H_{15}ON$ requires C, 79·9; H, 6·6; N, 6·2%; equiv., 225). Sperber *et al.* (*loc. cit.*) reported this compound as an oil, n_D^{25} 1·5830.

Acylation.—*2-Phenacylpyridine with acid anhydrides and acyl halides.* The sodio-derivative of 2-phenacylpyridine (0·005 mole) was treated with the acid anhydride or aroyl halide (0·006 mole) as described under "Alkylation." The products were crystallised from ethanol.

Acetic anhydride (50°; 0·5 hr.; toluene) gave α-*acetoxy*-β-2′-*pyridylstyrene* (II; R = Ac) (74%), yellow prisms, m. p. 94° (Found: C, 75·0; H, 5·4; N, 5·8%; equiv., 242. $C_{15}H_{13}O_2N$ requires C, 74·9; H, 5·4; N, 5·95%; equiv., 239). Hydrolysis of the enol ester with 2N-sulphuric acid gave 2-phenacylpyridine. It gave a *picrate*, yellow prisms, m. p. 159° (Found: C, 53·8; H, 3·5; N, 12·1%; equiv., 468. $C_{21}H_{16}O_9N_4$ requires C, 53·4; H, 3·4; N, 12·0%; equiv., 468).

Benzoic anhydride (50°; 2 hr.; acetone–toluene) gave 1 : 3-diphenyl-2-2′-pyridylpropane-1 : 3-dione (I; R = Bz) (75%), light yellow needles, 141·5° (Found: C, 79·4; H, 5·0; N, 4·9. Calc. for $C_{20}H_{15}O_2N$: C, 79·7; H, 5·0; N, 4·7%). Kloppenburg and Wibaut (*Rec. Trav. chim.*, 1946, **65**, 393) reported a compound, m. p. 140°, as a by-product (0·07% yield) from the reaction of benzoic anhydride on 2-picolyl-lithium.

p-Nitrobenzoyl chloride (50°; 2 hr.; toluene) gave 1-p-*nitrophenyl*-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione* (I; R = CO·C_6H_4·NO_2-*p*) (75%), yellow needles, m. p. 165° (Found: C, 69·6; H, 4·1; N, 7·9. $C_{20}H_{14}O_4N_2$ requires C, 69·4; H, 4·05; N, 8·1%).

3 : 5-Dinitrobenzoyl chloride (50°; 2 hr.; acetone–toluene) gave 1-(3 : 5-*dinitrobenzoyl*)-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione* (60%), yellow clusters of needles, m. p. 117—118° (Found: C, 60·7; H, 3·15; N, 10·9. $C_{20}H_{12}O_6N_3$ requires C, 61·4; H, 3·1; N, 10·7%).

1-p-*Chlorophenyl*-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione.*—*Method* A. *p*-Chlorobenzoyl chloride (1·05 g., 0·006 mole) and the sodio-derivative of 2-phenacylpyridine (from 1 g., 0·005 mole), heated for 2 hr. at 50° in toluene, yielded 1-p-*chlorophenyl*-3-*phenyl*-2-2′-*pyridylpropane*-1 : 3-*dione* (75%), pale yellow prisms, m. p. 126—126·5° (Found: C, 71·3; H, 4·2; N, 4·15. $C_{20}H_{14}O_2NCl$ requires C, 71·6; H, 4·2; N, 4·2%).

Method B. 2-Chlorophenacylpyridine (1·2 g., 0·005 mole) and sodamide (0·27 g.), heated at 80° for 3 hr. in toluene (15 ml.), gave a yellow flocculent precipitate of the sodio-derivative. Benzoic anhydride (1·36 g., 0·006 mole) in acetone (15 ml.) was added to the cooled suspension at 0° and the mixture heated at 50° for 2 hr. This gave 1-*p*-chlorophenyl-3-phenyl-2-2′-pyridylpropane-1 : 3-dione (70%), pale yellow prisms, m. p. 126° (Found: C, 71·1; H, 4·15; N, 4·3%).

The compounds prepared by methods A and B were shown to be identical by mixed m. p. and ultra-violet absorption spectra.

When the above diones were heated with picric acid in ethanol they gave 2-phenacylpyridine picrate (identity checked by mixed m. p. and equiv. wt. determinations).

Other Materials.—2-Phenacylpyridine and 1-2′-pyridyl-butan-2-one, and -pentan-2-one were prepared according to Levine *et al.* (*loc. cit.*). 2-*p*-Chlorophenacylpyridine, prepared by the same method (68% yield), had m. p. 89° (cf. Smith, Stewart, Roth, and Northey, *J. Amer. Chem. Soc.*, 1948, **70**, 3997).

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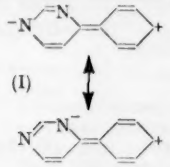
The Effects of Substitution on the Ultra-violet Absorption Spectra of Phenylpyrimidines.

By PETER B. RUSSELL.

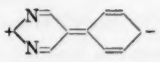
[Reprint Order No. 5260.]

The spectra of 2- and 4-amino- and 2 : 4-diamino-5- and -6-phenylpyrimidines are described. The changes in the spectra resulting from (*a*) replacement of the 2-amino-group by a hydroxyl or mercapto-group, (*b*) substitution in the pyrimidine ring adjacent to the phenyl group, and (*c*) substitution in the phenyl group, are reported. An attempt is made to interpret the observations on the basis of the valency bond resonance concept of the absorption of light.

IN a previous communication (Maggiolo and Russell, *J.*, 1951, 3297), it was shown that the absorption spectra of 5- and 6-phenylpyrimidines could be interpreted if the assumption was made that the forms (I) and (II) made large contributions to the excited states. For any such conjugated resonance form to contribute to a state of a molecule the molecule must be essentially planar and it was shown that interference with the co-planarity of the pyrimidine and phenyl rings by substitution in the positions adjacent to their junction had a profound effect on the spectrum of the resulting compound.



(I)



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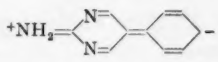

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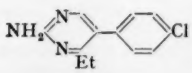


(IV)

The present communication deals with the effect on the spectra of these pyrimidines of substituents, in the 2- and/or the 4-position, capable of conjugation with the chromophoric system. The discussion centres chiefly on amino-compounds but reference is made on occasion to hydroxy- and mercapto-compounds. Braude, Jones, Koch, Richardson, Sondheimer, and Toogood (*J.*, 1949, 1890) restated the principles which govern the effect of substitution on the absorption spectra of organic compounds. The present paper follows these statements closely.

The introduction of 2-amino-group into a 5-phenylpyrimidine causes an increase in both the wave-length and the intensity of absorption (Table 1). A band at longer wave-length and with low intensity also appears. Such a substitution increases the conjugation, by incorporation of the amino-group into the conjugated system, as in (III), and thereby lowers the energy content of the resonance forms contributing mainly to the excited state, thus decreasing the excitation energy. The introduction of an ethyl group at the 6-position of the pyrimidine ring lowers both the wave-length and the intensity of the first band (conjugation band) of the spectrum and intensifies the second peak [see 2-amino-5-*p*-chlorophenyl-4-ethylpyrimidine (IV) in Table 1]. The introduction of the ethyl group does not

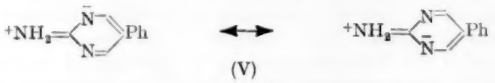
prevent the interannular conjugation but it appears to lessen it somewhat. This may be compared with the effect of an ethyl group on the spectrum of diphenyl (Braude, Sondheimer, and Forbes, *Nature*, 1954, **173**, 117). At the same time an increase in the

TABLE 1. *Absorption spectra of some amino-5-phenylpyrimidines.*

Pyrimidine	Absorption (mμ) (10^{-3} ε in parentheses)
5-Phenyl- [a]	Max. 256 (12·1)
2-Amino-5-phenyl-	Max. 263 (17·5); inflexion 300—320 (2·1)
2-Amino-5-*p*-chlorophenyl-4-ethyl-	Max. 252 (16·0); min. 295 (2·5); max. 305 (2·8)
4-Amino-5-phenyl-	Max. 248 (8·6); min. 270 (5·9); max. 282 (6·5)
2 : 4-Diamino-5-phenyl- [b]	Max. 256 (10·5); min. 277 (7·8); max. 294 (8·5)

[a] Maggiolo and Russell, *loc. cit.* [b] Russell and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763.

intensity of the long wave-length band is observed. Since this band coincides in wave-length with the bands seen in the spectra of 2-aminopyrimidines not having the 5-phenyl group it is believed to arise from considerable contributions from resonance forms such as (V) to transitions of the pyrimidine part of the molecule from the ground state to excited states. Thus when some hindrance is introduced, in addition to the whole molecule acting



(V)

as a conjugated chromophore each part exhibits its own chromophoric properties. Similar behaviour is reported for some diphenyls by Friedel, Orchin, and Reggel (*J. Amer. Chem. Soc.*, 1948, **70**, 199). The association of different bands in the spectrum with conjugated and unconjugated chromophores provides the key to the interpretation of the spectra of substituted phenylpyrimidines.

The spectra of both 4-amino- and 2 : 4-diamino-5-phenylpyrimidine (VI and VII) show two well-defined bands (Table 1). The origin of these is demonstrated by the introduction of another substituent in the pyrimidine or the phenyl ring adjacent to the ring junction. Thus 2 : 4-diamino-6-ethyl-5-phenylpyrimidine (VIII) shows only one band in its spectrum ($\lambda_{max.}$ 288 mμ, see Table 3), the shorter wave-length band of the conjugated chromophore having been eliminated. This type of spectrum is shown by all 5-phenylpyrimidines with a 4-amino-group and a 6-alkyl group (Table 2). Replacement of one of the *o*-hydrogen

TABLE 2. *Some hindered amino-5-phenylpyrimidines.*

5-Phenylpyrimidine	Absorption (mμ) (10^{-3} ε in parentheses)
2 : 4-Diamino-6-methyl-	Max. 240 (8·0); min. 265 (4·9); max. 288 (8·0)
2 : 4-Diamino-6-methyl-5-*p*-chloro-	Inflexion *ca.* 250 (9·0); min. 265 (800); max. 285 (9·9)
2 : 4-Diamino-6-ethyl-	Inflexion 250 (8·0); min. 265 (6·4); max. 288 (9·5)
2 : 4-Diamino-6-methyl-5-*o*-chloro [a]	Min. 260 (4·9); max. 288 (8·0)

[a] Russell and Hitchings, *loc. cit.*

TABLE 3. 2 : 4-*Diamino*-5-*o*-*substituted phenylpyrimidines.*

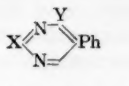
ortho-Substituent	Absorption (mμ) (10^{-3} ε in parentheses)
Hydrogen [a]	Min. 238 (5·5); max. 256 (10·5); min. 277 (4·8); max. 294 (8·5)
Fluorine	Min. 248 (5·8); max. 254 (4·5); min. 275 (5·9); max. 292 (7·0)
Chlorine [a]	Min. 249 (6·5); max. 255 (6·7); min. 272 (5·9); max. 292 (7)
Bromine	Min. 245 (5·5; broad; max. 292 (6·9)
Methyl (*p*-chlorophenyl)	Inflexion 250 (12·5); min. 275 (7·6); max. 290 (8·8)

[a] Russell and Hitchings, *loc. cit.*

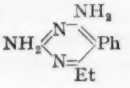
atoms of the benzene ring causes partial or complete loss of the conjugation band (Table 3). It is seen that when the substituent is fluorine or chlorine (IX) the effect is mainly on the intensity of this band with little or no alteration in wave-length, but when the much larger bromine is placed in this position the conjugation band is completely lost and the spectrum resembles that of 2 : 4-diaminopyrimidine with no aryl group at position 5 (Table 4). Since the effect of fluorine and chlorine is in the main on the intensity rather than on the

wave-length of absorption, the transitions must belong to the group described by Braude, Sondheimer, and Forbes (*loc. cit.*) as being between non-planar ground states and planar excited states. Such steric effects are looked upon as comparatively weak. Bromine has a much greater effect, as does an *o*-methyl group in conjunction with *p*-chloro (X). Guy (*J. Chim. phys.*, **1949**, **46**, 469) has calculated the effect of variations in the angle of twist (θ) on resonance conjugation in the diphenyl series. For values of θ between 0° and $\pi/8$ the conjugation is little affected; in the range $\pi/8$ to a value between $\pi/4$ and $3\pi/8$ it diminishes rapidly while for greater angles it is completely inhibited. Thus fluorine and chlorine must be placed in the first or second of these groups while bromine and methyl must fall in the third.

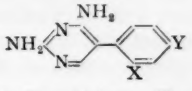
A comparison of the spectra of 2 : 4-diamino-6-methyl-5-phenylpyrimidine and its 5-*p*-chloro-analogue is interesting. The former shows a definite conjugation band ($\lambda_{max.}$ 240; Table 2) which is not shown by the latter. Since the *p*-chlorine atom cannot directly



(VI; X = H, Y = NH_2)
(VII; X = Y = NH_2)



(VIII)



(IX; X = Halogen, Y = H)
(X; X = Me, Y = Cl)

influence the steric situation at the ring junction the observed effect may be due either to electronic influences or to a repulsive force operating on the *o*-hydrogen atoms. If the methyl group is replaced by an ethyl group to give (VIII), the conjugation band is not visible. Braude, Sondheimer, and Forbes (*loc. cit.*) give figures from the diphenyl series which show the steric effect due to ethyl to be greater than that due to methyl. As might be expected, the spectrum of 2 : 4-diamino-5-*o*-chlorophenyl-6-methylpyrimidine (Table 2) is very similiar to that of a 2 : 4-diaminopyrimidine (Table 4). To summarise, one substituent in any of the four positions of a 5-phenylpyrimidine adjacent to the ring junction causes some loss of planarity in the ground state but less in the excited states. When two of these positions are substituted there is a gradation from little effect on the planarity of the excited state to complete loss of planarity in both states while three substituents cause a definite non-planar structure.

TABLE 4. *Absorption spectra of some simple aminopyrimidines.*

Pyrimidine	Absorption (mμ) (10^{-3} ε in parentheses)
2-Amino-	Max. <230 (>13); min. 251 (0·4); max. 296 (3·0)
4-Amino-	Max. 235 (11·5); min. 255 (2·9); max. 270 (3·8)
2 : 4-Diamino-6-methyl-	Max. *ca.* 230 (*ca.* 8·0); min. 253 (1·9); max. 280 (6·9)
2 : 4-Diamino-5-benzyl-6-methyl-	Max. <230 (>16); min. 260 (2·5); max. 288 (7·9)

When the 2-substituent of the pyrimidine ring is changed, the wave-length of the conjugation band increases in the series OH (250 mμ) < NH_2 (260 mμ) < SH (283 mμ). This is the reverse of the order of the electronegativities of the elements O, N, S (Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, New York, 1943, p. 60). This indicates the importance of structure (II) to the excited states where the atom attached to the 2-position carries a positive charge.

p-Substituents in the phenyl group also have an effect on the wave-length of the conjugation band (Table 5), but this is small except for the *p*-nitrophenyl compound. Here

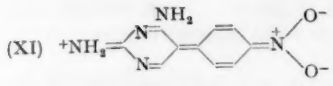
TABLE 5. *Effect of* para-*substituent on wave-length of conjugation band of 2 : 4-diamino-5-phenylpyrimidines.*

p-Substituent	OMe	H	Me	NH_2	Cl	Br	NO_2
$\lambda_{max.}$ (mμ)	259	260	260	265	268	270	345

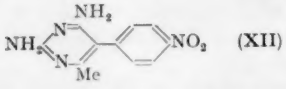
forms such as (XI) are possible. These structures have a favourable arrangement of electron-donor and electron-acceptor groups. Contributions from forms such as (XI) would be expected to lower the energy of the excited state considerably and so increase the wave-length of the conjugation band. Actually this band falls at 345 mμ in this case. The

origin of this band is demonstrated by introducing a substituent (methyl) in the 6-position. 2 : 4-Diamino-6-methyl-5-*p*-nitrophenylpyrimidine (XII) shows no band at this wavelength [XI : max. 230 (ε 13,400), 295 (ε 6500), 345 (ε 13,400); min. 272 (ε 2700), 311 mμ. XII : max. 231 (ε 13,200), 280 (ε 10,500); min. 255; inflexion 310—340 mμ (ε *ca.* 2500)].

Introduction of an amino-group into the 2- and/or 4-position of 4(6)-phenylpyrimidines causes different phenomena (Table 6). 4-Phenylpyrimidine shows only one intense band at



(XI)



(XII)

273 mμ (Maggiolo and Russell, *loc. cit.*), but 2-amino-4- and 4-amino-2-phenylpyrimidine do not show this band. In the last two compounds the spectrum is resolved into the usual two-banded form of an aminopyrimidine (cf. Table 4). Obviously in the 4(6)-phenylpyrimidines a 2- or 4-substituent cannot combine with the conjugated chromophore to lower the energy of the excited state; rather it favours excited states similar to (V) at the expense of forms such as (I). Since the spectrum owes little or nothing to interannular

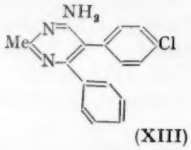
TABLE 6. *Some 4(6)-phenylpyrimidines.*

Pyrimidine	Absorption (mμ) (10^{-3} ε in parentheses)
4-Methyl-6-phenyl- [a]	Max. 243 (18·0)
2-Amino-4-methyl-6-phenyl-	Max. 240 (15·8); min. 278 (2·5); max. 315 (6·0)
2-Amino-5-cyano-4-phenyl- [b]	Max. 255 (23·1); min. 293 (3·2); max. 315 (4·0)
4-Amino-2-methyl-6-phenyl-	Max. 240 (27·0); min. 276 (6·0); max. 288 (7·0)
2 : 4-Diamino-6-phenyl-	Max. 240 (25·0); min. 270 (4·0); max. 305 (8·0)
2 : 4-Diamino-6-*p*-chlorophenyl- [c]	Max. 245 (16·0); min. 275 (2·0); max. 310 (4·0)

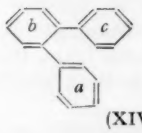
[a] Maggiolo and Russell, *loc. cit.* [b] Russell and Whittaker, *J. Amer. Chem. Soc.*, 1952, **74**, 1310. [c] Russell and Hitchings, *loc. cit.*

conjugation, steric hinderance to the coplanarity of the rings has little, if any, effect on the spectrum. The bands in the 4(6)-phenylpyrimidine spectra are all shifted slightly to the longer wave-lengths when compared with those of Table 4.

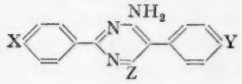
The spectra of some diphenylpyrimidines were also measured. 4-Amino-5-*p*-chlorophenyl-2-methyl-6-phenylpyrimidine (XIII) showed no evidence of conjugation between the rings [max. <230 (ε 27,000); min. 276 (ε 6500); max. 295 mμ (ε 7400)]. This is not surprising since the ultra-violet spectrum of *o*-terphenyl (XIV) shows no evidence of conjugation (Woods *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 3221). The lack of conjugation in *o*-terphenyl is readily understood: Karle and Brockway (*ibid.*, 1944, **66**, 1977) have shown, by electron-diffraction, that rings *a* and *c* are parallel and inclined to ring *b* at an angle of 45°.



(XIII)



(XIV)



(XV; X = Me, Y = Cl, Z = H)
(XVI; X = Y = H, Z = Me)

The spectrum of 4-amino-5-*p*-chlorophenyl-2-*p*-tolylpyrimidine (XV) shows a strong bifurcate conjugation band [max. 255 (ε 17,000), 267 (ε 16,400), 310 (ε 14,500); min. 262 (ε 16,200), 292 mμ (ε 12,500)]. 4-Amino-6-methyl-2 : 5-diphenylpyrimidine (XVI), on the other hand, shows a spectrum quite similar to that of (XIII), illustrating the steric effects of the 6-methyl group.

EXPERIMENTAL

Compounds.—The majority of the compounds used have been described previously (Russell and Maggiolo, *loc. cit.*; Russell and Hitchings, *loc. cit.*). 2 : 4-Diamino-5-benzyl-6-methylpyrimidine (Table 4) was described by Falco, Du Breuil, and Hitchings (*J. Amer. Chem. Soc.*,

1951, **73**, 3758). Other *compounds* not previously described were prepared by the application of well-known methods. They are listed in the annexed table.

No.	Pyrimidine	M. p.	Formula	Reqd. (%): C	Reqd. (%): H	Found (%): C	Found (%): H
1	2-Amino-5-*p*-chlorophenyl-4-ethyl-	168°	$C_{12}H_{12}N_3Cl$	61·7	5·1	61·9	5·3
2	2 : 4-Diamino-5-*o*-fluorophenyl-	163—164	$C_{10}H_9N_4F$	58·8	4·4	59·0	4·6
3	2 : 4-Diamino-5-(4′-chloro-2′-methylphenyl)-	209	$C_{11}H_{11}N_4Cl$	56·3	4·7	56·6	4·7
4	2-Amino-4-methyl-6-phenyl-	172—173	$C_{11}H_{11}N_3$	71·4	6·0	71·2	6·1
5	4-Amino-2-methyl-6-phenyl-	165	$C_{11}H_{11}N_3$	71·4	6·0	71·6	5·8
6	2 : 4-Diamino-6-phenyl-	162	$C_{10}H_{10}N_4$	64·5	5·4	64·7	5·1

(1) Prep. from 2-amino-5-*p*-chlorophenyl-6-ethyl-4-mercaptopyrimidine (Russell and Whittaker, unpublished work) by reduction with Raney nickel. (2) Prep. by the condensation of α-*o*-fluorophenyl-β-methoxyacrylonitrile with guanidine (cf. Russell and Hitchings, *loc. cit.*). (3) As (2), but from α-(4-chloro-2-methylphenyl)-β-methoxyacrylonitrile. (4) Prep. by the condensation of benzoylacetone and guanidine. (5) Prep. by chlorination and amination of the corresponding hydroxy-compound prepared by the condensation of ethyl benzoylacetate and acetamidine. (6) Prep. from 6-phenyl*iso*cytosine by chlorination and amination.

Spectra.—The ultra-violet absorption spectra were determined with a Beckman model DU quartz spectrophotometer (cell-length 1 cm.). The compounds were in solution (10 mg./l.) in ethanol.

The author thanks Miss Phoebe Lee Graham and Mr. W. Furcht for the determination of most of the spectra, and Mr. S. W. Blackman for the microanalyses.

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Studies in the Alicyclic Series. Part III. Michael Condensation of 1-Acetylcycloalkenes with cycloAlkanones.*

By W. J. ROSENFELDER and DAVID GINSBURG.

[Reprint Order No. 5311.]

Tricyclic αβ-ethylenic ketones may be obtained by Michael condensation of 1-acetyl*cyclo*alkenes with *cyclo*alkanones. These intermediates are of interest in the preparation of non-benzenoid aromatic systems.

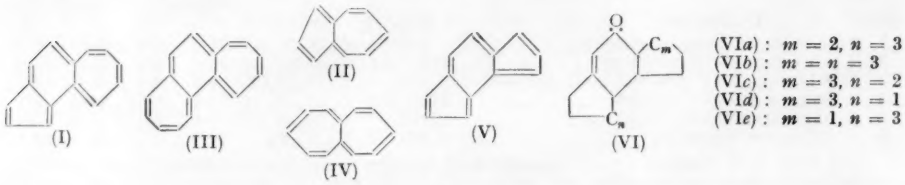
WHEN Dr. W. Taub brought to our attention the availability of 1-acetyl*cyclo*heptene of proven structure (Taub and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1952, **74**, 2117), it appeared that this substance would afford a promising starting point for the synthesis of certain non-benzenoid aromatic hydrocarbons. Thus, condensation of 1-acetyl*cyclo*heptene with *cyclo*pentanone might be expected to give rise to (VI*d*) which could be used for the synthesis of the vinylogous (or more precisely, the " butadienylogous ") analogue (I) of azulene (II); with *cyclo*heptanone it might give (VI*b*) which could be used for synthesis of the " butadienylogue " (III) of the still unknown heptalene (IV). These reactions were carried out in view of the analogies developed by Robinson *et al.* for the synthesis of various tricyclic systems (Rapson and Robinson, *J.*, 1935, 1287; cf. Crowfoot, Rapson, and Robinson, *J.*, 1936, 757; Hawthorne and Robinson, *J.*, 1936, 763; Linstead and Walpole, *J.*, 1939, 842).

In principle, one may arrive at a precursor of (I) by using 1-acetyl*cyclo*pentene and *cyclo*heptanone as the starting materials. Although the primary condensation product would be different from that obtained by condensing 1-acetyl*cyclo*heptene with *cyclo*pentanone, the final non-benzenoid hydrocarbon, if ultimately obtained, would be identical.

To complete the picture, it was decided, despite the known difficulties in working with 1-acetyl*cyclo*pentene and with *cyclo*pentanone in an alkaline medium (cf. Wallach, *Ber.*, 1896, **29**, 2955; Kon and Nutland, *J.*, 1926, 3106), to attempt to find conditions for the Michael condensation of these two components, as success in this case might lead to a

* Part II, *J. Amer. Chem. Soc.*, 1954, **76**, in the press.

precursor of indacene (V), of very great theoretical interest, which is the " butadienylogue " of the still unknown pentalene.



(VI*a*) : $m = 2, n = 3$
(VI*b*) : $m = n = 3$
(VI*c*) : $m = 3, n = 2$
(VI*d*) : $m = 3, n = 1$
(VI*e*) : $m = 1, n = 3$

In this communication, we report some of our observations in the preliminary stages of this project, namely, synthesis of (VI*a*—*e*). Further employment of these compounds, in direct and indirect dehydrogenation experiments, will be reported later.

The following Table summarises the light-absorption data (λ in Å; DNPH = dinitrophenylhydrazone).

	Ketones in EtOH		Oximes in EtOH		Semicarbazones in EtOH		2 : 4-DNPH's in $CHCl_3$	
	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε
(VI*a*)	2430	9660	2420	16,000	2705	15,700	3900	26,100
(VI*b*)	2410—2440	8600	2380—2420	11,800	2730	17,100	3900	28,000
(VI*c*)	2400	8500	2370	14,900	2680	24,800	3890	30,900
(VI*d*)	—	—	—	—	—	—	3880	32,000
(VI*e*)			2420—2440	11,600			3960	29,200

Michael condensation of the various 1-acetyl*cyclo*alkenes and *cyclo*alkanones proceeded satisfactorily with the exception of the condensation of 1-acetyl*cyclo*pentene and *cyclo*pentanone. Heating under reflux, in order to complete the dehydration of the aldol which is formed as an intermediate, is necessary, as it was shown in several cases that, when reflux periods shorter than those described in the Experimental section were used, some aldol was present in the product. Thus, for example, after an hour's reflux the infra-red spectrum of the product (VI*c*) showed, besides the band at 1675 $cm.^{-1}$ corresponding to the αβ-ethylenic ketone, bands at 3325 and 1711 $cm.^{-1}$ corresponding to the absorption of the intermediate ketol. When this impure product was heated in benzene with sodium methoxide for an additional hour, dehydration of the aldol was completed and pure αβ-ethylenic ketone was obtained. In this particular case, the intensity of absorption at 2400 Å rose from 7000 to 8500.

Experimental

Infra-red spectra were measured in $CHCl_3$, unless otherwise stated.

1-*Acetyl*cyclo*alkenes*.—1-Acetyl*cyclo*pentene was prepared by Hawthorne and Robinson's method (cf. Rapson and Robinson, *locc. cit.*). The fraction of b. p. 82—86°/48 mm. was used. A sample was converted into the semicarbazone and the free ketone was regenerated by refluxing with aqueous oxalic acid (45 min.), ether-extraction, and distillation. The ketone, b. p. 80—82°/33 mm., showed carbonyl absorption at 1660 $cm.^{-1}$.

1-Acetyl*cyclo*hexene was prepared by Christ and Fuson's method (*J. Amer. Chem. Soc.*, 1937, **59**, 893). The fraction of b. p. 195—200° was used. A pure sample, obtained by regeneration through the semicarbazone as described above, showed ketonic absorption at 1660 $cm.^{-1}$.

1-Acetyl*cyclo*heptene was prepared by the procedure of Taub and Szmuszkovicz (*loc. cit.*) except that the reaction was carried out at −20°. The fraction boiling at 207—215° was used. The yield reported was raised to 70% by using C.P. sodium carbonate for dehydrochlorination of the intermediate 1-acetyl-2-chloro*cyclo*heptane. A pure sample regenerated through the semicarbazone had b. p. 99—100°/30 mm. and showed ketonic absorption at 1657 $cm.^{-1}$.

Self-condensation of 1-*Acetyl*cyclo*pentene*.—A solution of 1-acetyl*cyclo*pentene (5·5 g.) and potassium *tert.*-butoxide (prepared from 2·1 g. of potassium) in dry benzene (25 ml.) was refluxed for 1 hr. After cooling, acetic acid (4 ml.) was added. The mixture was washed with water and distilled under reduced pressure. Two impure fractions, b. p. 135—160°/1 mm. (1·7 g.) and 160—220°/1 mm. (1·1 g.), were obtained, and a gummy residue (2·3 g.). Each of the fractions

consisted of material of varying degrees of polymerisation. No crystalline derivatives could be obtained.

Self-condensation of cyclo*Pentanone*.—A solution of *cyclo*pentanone (4·2 g.) and potassium *tert.*-butoxide (from 2 g. of potassium) in benzene (25 ml.) was refluxed for 1 hr. The mixture was worked up as described for 1-acetyl*cyclo*pentene. *cyclo*Pentylidene*cyclo*pentanone, b. p. 99—101°/2 mm. (1·6 g.), n_D^{20} 1·5262, was obtained. Wallach (*loc. cit.*) reports b. p. 117—119°/12 mm. and n_D^{20} 1·52095. The **2 : 4-*dinitrophenylhydrazone*** formed maroon needles, m. p. 222·5—223·5° (from ethyl acetate–ethanol) (Found : C, 58·1; H, 5·4; N, 16·9. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 17·0%). Light absorption in $CHCl_3$: $\lambda_{max.}$ = 3990 Å (ε 25,100). The oxime formed needles, m. p. 120—121° (from ethanol). Light absorption in EtOH : $\lambda_{max.}$ = 2560 Å (ε 11,400). Wallach (*loc. cit.*) reports m. p. 123—124°.

A second fraction (2·2 g.), b. p. 165—170°/2 mm., was obtained. This was **2 : 5-di*cyclo*pentylidene*cyclo*pentanone** and had m. p. 82·5—83·5° (from methanol) (Found : C, 83·5; H, 9·2. Calc. for $C_{15}H_{20}O$: C, 83·3; H, 9·3%). Wallach (*loc. cit.*) reports b. p. 190°/12 mm., m. p. 76—77°.

Self-condensation of cyclo*Heptanone*.—A solution of *cyclo*heptanone (5·6 g.) and potassium *tert.*-butoxide (from 2·1 g. of potassium) in dry benzene (25 ml.) was refluxed for 4·5 hr. The mixture was treated as above. Distillation afforded fractions including (*a*) *cyclo*heptanone, b. p. 180—185°/760 mm. (0·7 g.), and (*b*) *cyclo*heptylidene*cyclo*heptanone, b. p. 130—135°/0·9 mm. (2·6 g.), n_D^{19} 1·52122 [light absorption in EtOH : $\lambda_{max.}$ 2530 Å (ε 2870); infra-red absorption in CCl_4 : no OH band, 1688 cm.$^{-1}$ (–C=C–C=O); Godchot and Brun (*Compt. rend.*, 1922, **174**, 618) report b. p. 143—145°/8 mm., n_D^{14} 1·5144]. The **2 : 4-*dinitrophenylhydrazone*** of the latter formed yellow needles, m. p. 144—145° (from ethyl acetate–methanol) (Found : C, 62·0; H, 6·9; N, 14·7. $C_{20}H_{26}O_4N_4$ requires C, 62·2; H, 6·8; N, 14·5%). Upon admixture with *cyclo*heptanone 2 : 4-dinitrophenylhydrazone, m. p. 143—144° (from ethyl acetate–ethanol), the m. p. was depressed to 134—135°. Light absorption in $CHCl_3$: $\lambda_{max.}$ 3740 Å (ε 22,300).

2 : 3 : 4 : 5 : 7 : 8 : 9 : 10 : 11 : 4a : 11a : 11b-*Dodecahydro*-5-*oxo*-1H-cyclo*hepta*[a]*naphthalene* (VI*a*).—A solution of *cyclo*heptanone (5·6 g., 0·05 mole) in dry benzene (5 ml.) was added with swirling to a suspension of potassium *tert.*-butoxide [from 2·1 g. (0·0525 g.-atom) of potassium] in dry benzene (20 ml.). To this was immediately added a solution of 1-acetyl*cyclo*hexene (6·2 g., 0·05 mole) in dry benzene (5 ml.). The mixture became warm and the alkoxide slowly dissolved. To complete the reaction, the solution was refluxed for 2 hr. After cooling, acetic acid (4 ml.) was added, followed by water (20 ml.) and ether (50 ml.). The ether–benzene extract was washed twice with water and dried (Na_2SO_4), and the solvents were removed. The oily residue was distilled at reduced pressure, giving a forerun of unchanged ketones, b. p. 60—85°/30 mm. (2·5 g.). Upon distillation in a high vacuum and redistillation, the αβ-ethylenic *ketone*, b. p. 150—151°/0·9 mm. (6·1 g., 55·5%), n_D^{20} 1·5342, was obtained (Found : C, 82·4; H, 10·0. $C_{15}H_{22}O$ requires C, 82·5; H, 10·2%). Infra-red absorption : 1666 cm.$^{-1}$ (–C=C–C=O). The *oxime* formed colourless prismatic needles, m. p. 198·5—199·5° (from ether) (Found : C, 77·0; H, 9·9; N, 6·2. $C_{15}H_{23}ON$ requires C, 77·2; H, 9·9; N, 6·0%). The *semicarbazone* crystallised in colourless needles, m. p. 189—190° (from methanol–chloroform) (Found : C, 70·3; H, 9·9; N, 15·3. $C_{16}H_{25}ON_3$ requires C, 69·8; H, 9·2; N, 15·3%). The orange **2 : 4-*dinitrophenylhydrazone*** had m. p. 196—197° (from ethyl acetate–ethanol) (Found : C, 62·8; H, 6·7; N, 14·4. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·6; N, 14·1%).

2 : 3 : 4 : 6 : 7 : 8 : 9 : 10 : 11 : 6a : 11a : 11b-*Dodecahydro*-6-*oxo*-1H-cyclo*hepta*[a]*naphthalene* (VI*c*).—The condensation of 1-acetyl*cyclo*heptene with *cyclo*hexanone was carried out as described above, using the corresponding molar quantities of reactants. The αβ-ethylenic *ketone* (VI*c*) had b. p. 149—152°/0·8 mm. (6 g., 54·5%) (Found : C, 82·1; H, 10·5%). Infra-red absorption : 1675 cm.$^{-1}$ (–C=C–C=O). The *oxime* formed long colourless rectangular plates, m. p. 164—165° (from ethyl acetate) (Found : C, 76·9; H, 9·8; N, 5·3%). The colourless *semicarbazone* crystallised in needles, m. p. 110—111° (from methanol–chloroform), m. p. 194—195° after drying at 100°/2 mm. for 2 hr. (Found : C, 70·2; H, 9·8; N, 15·1%). The bright orange **2 : 4-*dinitrophenylhydrazone*** formed shiny prisms, m. p. 200—200·5° (from ethyl acetate–methanol) (Found : C, 62·8; H, 6·6; N, 14·3%).

1 : 2 : 3 : 4 : 5 : 6 : 8 : 9 : 10 : 11 : 12 : 5a : 12a : 12b-*Tetradecahydro*-6-*oxodi*cyclo*hepta*[a,c]-*benzene* (VI*b*).—The condensation of 1-acetyl*cyclo*heptene with *cyclo*heptanone was carried out as described above, using the corresponding molar quantities of reactants. The αβ-ethylenic *ketone* (VI*b*) had b. p. 166—167°/0·4 mm. (6·2 g., 57%), $n_D^{20·3}$ 1·5346 (Found : C, 82·1; H, 10·1. $C_{16}H_{24}O$ requires C, 82·7; H, 10·4%). Infra-red absorption in CCl_4 : 1668 cm.$^{-1}$. The *oxime* formed fine colourless needles, m. p. 157·5—158·5° (from ethyl acetate) (Found : C, 78·2; H,

10·3; N, 5·5. $C_{16}H_{25}ON$ requires C, 77·7; H, 10·2; N, 5·7%). The *semicarbazone* crystallised in colourless needles, m. p. 182—183° (from methanol–chloroform) (Found: C, 70·8; H, 10·2; N, 14·6. $C_{17}H_{27}ON_3$ requires C, 70·6; H, 9·4; N, 14·5%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 190—191° (from ethyl acetate–methanol) (Found: C, 63·8; H, 6·3; N, 13·8. $C_{22}H_{28}O_4N_4$ requires C, 64·1, H, 6·8; N, 13·6%).

1 : 2 : 3 : 4 : 6 : 7 : 8 : 9 : 10 : 3a : 10a : 10b-*Dodecahydro*cyclo*hept*[e]*inden*-4-*one* (VI*e*).—The following conditions were found to be the most satisfactory: Potassium *tert.*-butoxide (from 2·1 g. of potassium) was covered with dry benzene (30 ml.), and the mixture was cooled to 5°. A cold solution (5°) of *cyclo*heptanone (5·6 g.) in dry benzene (10 ml.) was added with stirring, followed by a cold solution (5°) of 1-acetyl*cyclo*pentene (5·5 g.) in dry benzene (10 ml.). The solution was kept at 5° for an additional hr. The alkoxide dissolved completely after the first 20 min. of stirring. The solution was refluxed for 20 min., then cooled, acetic acid (4 ml.) was added, and the whole was worked up as usual. During distillation, considerable resinification occurred, but a fraction containing the desired αβ-ethylenic ketone (VI*e*), b. p. 146—150°/1·2 mm (4·2 g., 41%), was isolated (infra-red absorption in CCl_4: 1662 cm.$^{-1}$) and characterised by means of the *oxime*, colourless needles, m. p. 187·5—188·5° (Found: N, 6·2. $C_{14}H_{21}ON$ requires N, 6·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised as dark-red needles, m. p. 147—148°, from ethyl acetate–methanol (Found: C, 62·0; H, 6·2; N, 15·0. $C_{20}H_{24}O_4N_4$ requires C, 62·5; H, 6·3; N, 14·6%).

Conditions similar to those used for the condensation of 1-acetyl*cyclo*hexene with *cyclo*heptanone (see above) afforded the ketone in only 24% yield.

1 : 2 : 3 : 5 : 6 : 7 : 8 : 9 : 10 : 5a : 10a : 10b-*Dodecahydro*cyclo*hept*[e]*inden*-5-*one* (VI*d*).—Owing to the ready self-condensation of *cyclo*pentanone in the presence of alkali-metal alkoxides, considerable difficulties were encountered in this reaction. The conditions found to be most satisfactory were the following: Sodium methoxide (2·83 g., 0·0525 mole) was covered with dry benzene (30 ml.); the mixture was cooled to 5° and stirred vigorously. A mixture of *cyclo*pentanone (4·2 g.) and 1-acetyl*cyclo*heptene (6·9 g.) in dry benzene (10 ml.) was cooled to 5° and added in one portion. The mixture was stirred for 35 min. at 5° and acetic acid (4 ml.) was added. After the usual working up and removal of a forerun at 30 mm., a fraction, b. p. 150—170°/1 mm. (2·1 g.), was collected. Redistillation of this fraction did not lead to much improved fractionation and the material boiled over a 20° range. This fraction, n_D^{20} 1·5357 (infra-red absorption in CCl_4: 1667 cm.$^{-1}$), was undoubtedly contaminated with di*cyclo*pentylidene*cyclo*pentanone but gave the 2 : 4-*dinitrophenylhydrazone* of the αβ-ethylenic ketone (VI*d*), which crystallised as dark red plates, m. p. 157—159° (from ethyl acetate–methanol) (Found: C, 62·5; H, 6·4; N, 14·7. $C_{20}H_{24}O_4N_4$ requires C, 62·5; H, 6·3; N, 14·6%).

When potassium *tert.*-butoxide was used in the condensation, as described above for the condensation of 1-acetyl*cyclo*pentene with *cyclo*heptanone, employing 0·05 molar quantities of reactants, the fraction of b. p. 150—170°/1 mm. was again obtained (1·8 g.).

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Liquid-phase Reactions at High Pressures. Part VIII. The Kinetics of an "* ortho-*Effect" Reaction at High Pressures.*

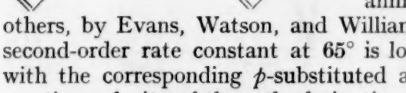
By K. E. Weale.

[Reprint Order No. 5346.]

The rate of the reaction between methyl iodide and *o*-methyl-*NN*-dimethylaniline in dry methanol has been measured up to 5000 atmospheres at four temperatures. This reaction, which exhibits the "*ortho*-effect," is accelerated by pressure. The changes in the Arrhenius parameters, A and E, are, however, the reverse of those found for unhindered Menschutkin reactions, which are also accelerated by pressure. It is concluded that a new effect is operative, and that pressure assists this reaction by reducing steric strain in the transition state.

At hydrostatic pressures of several thousand atmospheres the rates of many liquid-phase reactions are considerably increased. Previous measurements (Perrin, *Trans. Faraday Soc.*, 1938, **34**, 144; Newitt, Sapiro, *et al.*, Parts III and V, *J.*, 1938, 784; 1939, 1761) have shown that the acceleration is greatest for the so-called "slow" reactions, in which the A term of the Arrhenius equation, $k = Ae^{-E/RT}$, is smaller by several powers of ten than the value ($\sim 10^{12}$) characteristic of "normal" reactions.

Rate determinations have now been carried out at high pressures on a "slow" reaction of a type which is retarded at ordinary pressure by the "*ortho*-effect." This is the Menschutkin reaction between methyl iodide and *o*-methyl-*NN*-dimethylaniline in dry methanol, which was investigated, with others, by Evans, Watson, and Williams (*J.*, 1939, 1345, and 1348) who find that the second-order rate constant at 65° is lower by a factor of 61 than that for the reaction with the corresponding *p*-substituted amine at the same temperature. The decreased reaction velocity of the *ortho*-derivative is due to an increase of 6·6 kcal./mole in the activation energy E which outweighs an accompanying 250-fold increase in A.



Experimental

Apparatus.—The equipment for producing pressures up to 5000 atm. has been described by Newitt *et al.* (*J.*, 1938, 784). The pressure vessel is a steel, compound-shrunk cylinder which is immersed in an oil-bath maintained at a constant temperature to within ±0·1°. It is sealed at the top by a hard-rubber closure and a steel screw-plug. Steel capillary tubing leads from the base to a piston intensifier with an effective intensification ratio of 9·1 : 1, and the pressure-transmitting medium is liquid paraffin, which completely fills the apparatus. The Pyrex-glass reaction tube (capacity 4—5 ml.), closed at the top by a ground-glass stopper and open at the bottom, floats on mercury in a steel holder. The mercury transmits pressure to the reactants and prevents contamination by the oil.

Materials.—"AnalaR" methanol was dried by the Lund–Bjerrum magnesium method (*Ber.*, 1931, **64**, 210), fractionated in a Widmer column (b. p. 64·2—64·5°/760 mm.), and stored in a desiccator. Methyl iodide and *o*-methyl-*NN*-dimethylaniline were treated as described by Evans, Watson, and Williams, and fractionated at normal pressure (b. p. 42·5° and 184—185°, respectively). 0·2M-Solutions of each reactant in methanol were stored in 100 ml. stoppered flasks in a desiccator in the dark.

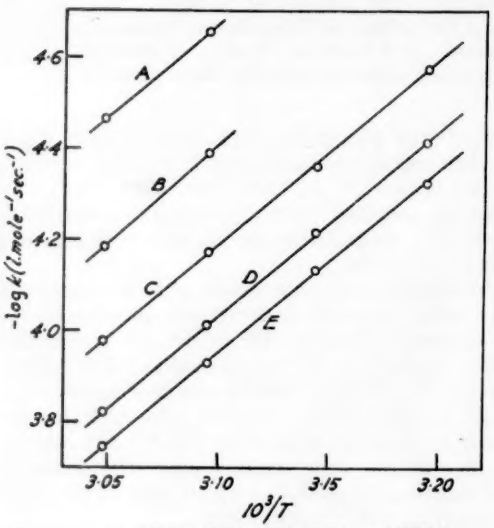
Kinetic Measurements.—5 ml. of each methanolic solution were mixed and the reaction tube was filled and put in the holder which was then enclosed in the pressure vessel (already at a constant temperature); pressure was then developed by means of the oil hand-pump and intensifier. This operation took 1—2 min., and the time of a run was usually 300—500 min. Pressure was measured on the low-pressure side of the intensifier by a Bourdon-tube gauge calibrated against a free-piston gauge. The pressure in the reaction vessel was calculated from the effective ratio of the intensifier, also calibrated by a free-piston gauge. The accuracy of the pressure measurement was about 0·1%, and the pressure was held constant within ±1%.

* Part VII, *J.*, 1952, 2223.

At the end of a run, the pressure was reduced quickly to 1 atm. and the solution removed. 2 ml. were added to 25 ml. of "AnalaR" light petroleum (b. p. 40—60°) and extracted three times with 10 ml. portions of distilled water. The aqueous extract was acidified with 5—10 drops of dilute acetic acid, and titrated with 0·01N-silver nitrate (eosin).

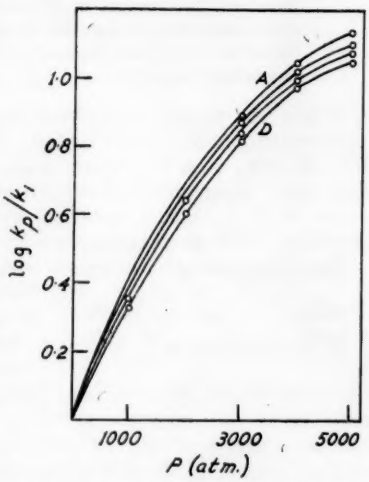
Several runs were carried out at each pressure and temperature. Bimolecular rate constants were calculated and average values taken. The maximum variation in k was generally 2—3%. Runs carried out with the addition of a drop of water (about 0·05% by weight) did not give significantly different rates, showing that the reaction is not sensitive to small amounts of moisture.

FIG. 1.



Curves A—E at 1000, 2000, 3000, 4000, *and* 5000 *atm. respectively.*

FIG. 2.



Curves A—D at 40°, 45°, 50°, *and* 55° *respectively.*

Results.—The rate constants were measured at 1000 atm. intervals up to 5000 atm., at 40°, 45°, 50°, and 55°, except that at the lowest two pressures the reaction was sufficiently fast only at 50° and 55°.

The velocity constant k_1 was also measured in the same apparatus at 1 atm. at 50°. The result, together with Evans, Watson, and Williams's values at 65°, 90°, and 100°, gives a good straight line for log k against $1/T$. Velocity constants at 1 atm. for the other three reaction temperatures were taken from this line.

TABLE 1. *Bimolecular velocity constants* (*l. mole*$^{-1}$ *sec.*$^{-1}$) $\times 10^5$, *at various pressures and temperatures.*

Temp.	40°	45°	50°	55°
Velocity constant at 1 atm., k_1	0·347	0·587	0·986	1·61

Temp.	k'	k	k_p/k_1	Temp.	k'	k	k_p/k_1
	1000 atm.				4000 atm.		
50°	2·41	2·22	2·25	40°	4·71	3·88	11·2
55	3·76	3·45	2·14	45	7·49	6·15	10·5
				50	11·9	9·75	9·89
	2000 atm.			55	18·6	15·2	9·41
50°	4·70	4·11	4·17				
55	7·38	6·43	3·99		5000 atm.		
				40°	5·79	4·78	13·8
	3000 atm.			45	8·94	7·39	12·6
40°	3·15	2·67	7·69	50	14·2	11·8	12·0
45	5·18	4·38	7·46	55	21·7	18·1	11·2
50	8·02	6·77	6·87				
55	12·5	10·5	6·55				

All the rate constants have been corrected for thermal expansion, and for the isothermal compression of the solvent at the reaction temperature (about 15% at 5000 atm.). The compression data used were those of Bridgman (*Proc. Amer. Acad. Arts Sci.*, 1913, **49**, 3), which may be slightly too low (Gibson, *J. Amer. Chem. Soc.*, 1935, **57**, 1551), but not enough to affect this correction. The results are shown in Table 1, where k' is the temperature-corrected constant, and k is the final value corrected for compression. k_p/k_1 is the ratio of the rate constant at high pressure to that at 1 atm.

In Fig. 1, $\log_{10} k$ is plotted against $1/T$. Except for 1000 and 2000 atm. the straight lines have been fitted by the method of least squares, and the corresponding Arrhenius parameters are given in Table 2. The effect of pressure on E and A is always to diminish them, although the variation of each with pressure is not quite regular because of experimental error. The accelerating effect falls off markedly at high pressures as is illustrated in Fig. 2, where $\log_{10} k_p/k_1$ is plotted against P.

TABLE 2. *Arrhenius parameters at various pressures.*

P (atm.)	1	1000	2000	3000	4000	5000
$\log_{10} A$	9·129	(8·0)	(8·4)	8·40	8·53	7·97
E (kcal./mole)	20·89	(18·7)	(18·9)	18·57	18·53	17·60

(The figures at 1000 and 2000 atm. are obtained from rates at two temperatures only.)

DISCUSSION.

The reaction studied is accelerated by pressure to much the same extent as are others of the Menschutkin type examined by Perrin and his co-workers. There is, however, a notable difference in the effect on A and E. In each of seven reactions Perrin finds the increase in rate to be due to a large increase in A (up to 111-fold at 3000 atm.), which outbalances a simultaneous increase in E (up to 1·4 kcal. at 3000 atm.). In the present case, on the contrary, there is a considerable decrease in E, which is partially offset by a decrease in A. This reversal of behaviour among reactions of similar type is thought to indicate a fundamental difference in the way in which pressure influences the reaction rate.

The "Transition-density" Theory.—The effect of hydrostatic pressure on the rate of reaction in a liquid has been related to the volume change ΔV^*, accompanying formation of the transition state, by the equation :

$$\partial \log k/\partial P = \Delta V^*/RT$$

(Evans and Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 875; 1936, **32**, 1333; Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, 1941; Stearn and Eyring, *Chem. Reviews*, 1941, **29**, 509). ΔV^* may be obtained at any pressure from the slope of the curve relating $\log k_p/k_1$ to P, which for some reactions is a straight line. The pressure dependence of the reaction rate thus gives information about the density of the transition state, as the temperature dependence gives the energy. Evans and Polanyi pointed out that ΔV^* includes a term representing the different amount of interaction of the solvent with the reactants and with the transition state. This aspect has been re-emphasised by Buchanan and Hamann (*Trans. Faraday Soc.*, 1953, **49**, 1425), and in Menschutkin reactions, in which charge separation occurs, with consequent electrostriction of solvent molecules, the solvation term may predominate.

The reversed effect of pressure on E and A, which shows the operation of a new factor in the "*ortho*-effect" reaction, is not readily explicable by means of the "transition-density" theory.

The Nature of the "ortho-*effect.*"—Evans, Watson, and Williams could find no connection between the magnitude of the "*ortho*-effect" in Menschutkin reactions and the weights, volumes, or chemical characters of different substituent groups. Considering also the absence of a large "*ortho*-effect" in the basic strengths of the isomeric methyl-*NN*-dimethylanilines, Watson suggested that the effect is only operative in the highly energised transition state, and that it is due to interaction of the *ortho*-group with the unshared nitrogen electrons. The interaction may vary from near zero (*o*-fluoro) to proton-transfer with electrovalent bonding (*o*-carboxyl). In the case of the *o*-methyl group, Watson assumes hydrogen-bond formation with the nitrogen atom. W. G. Brown and Fried (*J. Amer. Chem. Soc.*, 1943,

65, 1841), however, correlate Watson's sequence of the relative "*ortho*-effects" of different substituent groups with their effectiveness in preventing rotation in the diphenyl series. They suppose that the *N*-methyl groups and the aromatic ring have to become coplanar in the transition state, and that the "*ortho*-effect" is due to steric hindrance in this configuration. Confirmatory evidence is provided by the absence of the effect in the reactions of bicyclic tertiary amines, in which the groups are constrained into coplanarity.

H. C. Brown (Brown and Barbaras, *J. Amer. Chem. Soc.*, 1947, **69**, 1137; Brown and Eldred, *ibid.*, 1949, **71**, 445; Brown and Cahn, *ibid.*, 1950, **72**, 2939) also supports a steric rather than a polar interpretation. The absence of a large "*ortho*-effect" in the base strengths is attributed to the small steric requirements of the proton, and the differences of stability found among the compounds of trimethylboron with pyridine and the picolines show that the "*ortho*-effect" does appear in equilibria. Brown and Barbaras conclude that the slowness with which *ortho*-substituted compounds participate in displacement reactions is due to steric strain in the transition state. This strain will result in an increased activation energy, as was found in the sterically hindered S_N2 reactions of *neo*pentyl halides by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 157 *et seq.*).

The Acceleration of the "ortho-*Effect*" *Reaction by Pressure.*—The alterations in A and E caused by pressure are such as to oppose the increase in these parameters, which occurs at ordinary pressure when one changes from the *para*- to the *ortho*-substituted amine. They are the reverse of the pressure effects found for the Arrhenius parameters of unhindered Menschutkin reactions. For these reasons it is concluded that in the "*ortho*-effect" reaction the compression energy of the liquid system is able to contribute directly to lowering the activation energy by overcoming steric strain in the transition state. The "steric strain" effect, and not that of "transition-density," is the principal factor causing an increase in the rate constant.

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The Constitution of Yohimbine and Related Alkaloids. Part VIII. Synthesis of 3-Ethyl-2-(5-ethyl-2-pyridyl)indole, a Degradation Product of Corynantheine.*

By R. M. Anderson, G. R. Clemo, and G. A. Swan.

[Reprint Order No. 5370.]

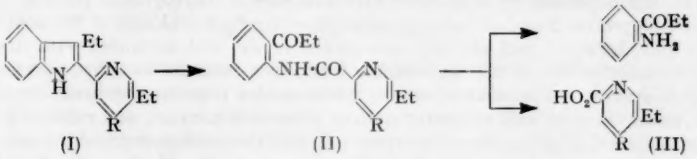
3-Ethyl-2-(5-ethyl-2-pyridyl)indole (I; R = H) and 5-ethylpyridine-2-carboxylic acid (III; R = H), degradation products of corynantheine, have been synthesised and shown to be identical with the products of natural origin.

The alkaloid corynantheine, on dehydrogenation with selenium, gives two oxygen-free products, alstyrine (coryline) which probably has structure (I; R = Et) (Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390), and de-ethylalstyrine (de-ethylcoryline) (I; R = H) (Janot and Goutarel, *Bull. Soc. chim.*, 1951, 588). Ozonolysis of de-ethylalstyrine (Janot and Goutarel, *loc. cit.*) yields the amide (II; R = H) which on acid hydrolysis gives *o*-aminopropiophenone and an ethylpyridinecarboxylic acid which was formulated by Janot and Goutarel (*loc. cit.*) as (III; R = H), because of its decarboxylation to 3-ethylpyridine, although it might conceivably be 3-ethylpyridine-2-carboxylic acid.

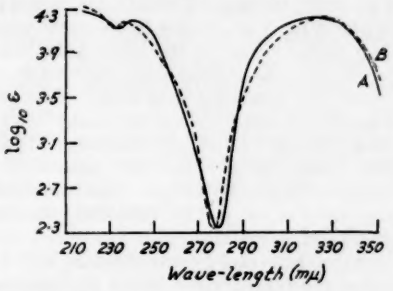
The syntheses of 5-ethylpyridine-2-carboxylic acid (III; R = H) and of 3-ethyl-2-(5-ethyl-2-pyridyl)indole were therefore undertaken. Mild oxidation of 5-ethyl-2-styrylpyridine (cf. Clemo and Gourlay, *J.*, 1938, 478, for the oxidation of the 2-styryl derivative of 2 : 4-lutidine) gave 5-ethylpyridine-2-carboxylic acid identical with the acid of natural origin. Decarboxylation of the synthetic acid with copper powder gave 3-ethylpyridine. The ester of (III; R = H), on condensation with ethyl butyrate under Claisen conditions

* Part VII, *J.*, 1954, 2579.

and subsequent hydrolysis, gave 2-butyryl-5-ethylpyridine, the phenylhydrazone of which underwent a Fischer indole reaction to give (I; R = H). This base readily formed a crystalline picrate, styphnate, and hydrochloride; the melting points of our picrate and



hydrochloride, which were determined in capillary tubes, differ from those reported by Janot and Goutarel, but Professor Janot informs us that the values he records were determined on the Maquenne block. From the crude picrate of de-ethylalstyrine of natural origin we have prepared the pure picrate and styphnate which proved to be



Ultra-violet absorption spectra of (*A*) ——— *natural and* (*B*) ---- *synthetic de-ethylalstyrine hydrochloride.*

identical with the corresponding synthetic derivatives. The ultra-violet absorption spectra of the synthetic and natural hydrochlorides showed a great similarity (see Figure) and were characteristic of an indole nucleus conjugated with a pyridine nucleus.

Experimental

Ultra-violet absorption measurements were made in ethanol with a Hilger " Uvispec " spectrophotometer.

5-Ethyl-2-styrylpyridine.—5-Ethyl-2-methylpyridine (Frank, Blegen, Dearborn, Myers, and Woodward, *J. Amer. Chem. Soc.*, 1946, **68**, 1368; purified *via* the picrate, m. p. 164°) (35 g.), freshly distilled benzaldehyde (70 g.), and acetic anhydride (70 g.) were refluxed together for 48 hr. The mixture was made acid to Congo-red with 1 : 1 hydrochloric acid, steam-distilled to remove excess of benzaldehyde, and, while being cooled in ice, basified with 15% sodium hydroxide solution. The dark brown crystals were collected, washed with cold water, and recrystallised from light petroleum (b. p. 40—60°) (charcoal), giving the *styryl* derivative as colourless prisms (35 g.), m. p. 58—59° (Found : C, 86·3; H, 7·2. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2%). The *picrate* separated from ethanol in long, pale yellow needles, m. p. 203—204° (Found : C, 57·4; H, 4·1. $C_{15}H_{15}N,C_6H_3O_7N_3$ requires C, 57·3; H, 4·1%).

5-Ethylpyridine-2-carboxylic Acid (III; R = H).—A solution of the above styryl compound (18 g.) in acetone (180 ml.) was cooled in ice and stirred while finely powdered potassium permanganate (39 g.) was added during 30 min. The manganese dioxide formed was removed by filtration, washed with acetone, and extracted with hot water (3 × 180 ml.). The aqueous filtrate was acidified with dilute hydrochloric acid and kept at room temperature for 1 hr. The precipitated benzoic acid (5·8 g.) was removed, and the filtrate was warmed and stirred while copper carbonate (8 g.) was added. The solution was cooled overnight, and the blue crystalline *copper* salt was collected, washed with water, and dried (Found : C, 53·0; H, 4·6; N, 7·3. $C_{16}H_{16}O_4N_2Cu$ requires C, 52·75; H, 4·4; N, 7·7%), suspended in hot water, and treated with hydrogen sulphide. The copper sulphide was filtered off, and the filtrate rapidly evaporated to dryness on the water-bath under reduced pressure, giving the *acid* (5 g.) as colourless needles, m. p. 101—102° (Found : C, 64·0; H, 6·2; N, 9·6. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%). The acid (III; R = H) of natural origin had m. p. 100—101° alone or mixed with our synthetic acid.

Decarboxylation of 5-Ethylpyridine-2-carboxylic Acid.—The synthetic acid (10 mg.) was intimately mixed with copper powder (0·6 mg.) and gently heated. The distillate was disolved in ether, and picric acid in ether was added. The picrate (long, yellow needles from methanol) had m. p. 125° not depressed by admixture with authentic 3-ethylpyridine picrate.

Ethyl 5-Ethylpyridine-2-carboxylate.—A solution of the hydrochloride of the acid (III; R = H) (5 g.) in anhydrous ethanol (40 ml.) was cooled in ice, and saturated with dry hydrogen chloride. The solution was gently warmed for 1 hr., then refluxed for 1 hr., and kept at room temperature overnight. The ethanol was removed under reduced pressure, the residue was dissolved in water, basified with saturated sodium carbonate solution, and extracted with ether. The extract was dried (K_2CO_3), the ether removed, and the residue distilled, giving the colourless *ester* (3·5 g.), b. p. 140—142°/16 mm. (Found: C, 67·3; H, 7·4. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%). The *picrate* prepared in ether formed yellow needles, m. p. 107—108° (Found: C, 47·3; H, 3·8. $C_{10}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 47·1; H, 3·9%).

2-Butyryl-5-ethylpyridine.—To a suspension of potassium ethoxide (from potassium, 0·2 g.) in anhydrous benzene (15 ml.) was added the foregoing ester (0·65 g.), followed by ethyl butyrate (1·2 g., 100% excess). The mixture, which immediately became red-brown, was refluxed on the water-bath for 5 hr., cooled in ice-water while hydrochloric acid (2 : 1; 15 ml.) was added, and heated under reflux on the water-bath overnight, then evaporated to dryness under reduced pressure, and the residue was dissolved in water, basified with saturated potassium carbonate solution, and extracted with ether. The extract was dried (K_2CO_3), the solvent removed, and the residue distilled, giving the *ketone* (0·3 g.) as a colourless oil, b. p. 88—91°/2 mm. (Found: C, 74·4; H, 8·6. $C_{11}H_{15}ON$ requires C, 74·6; H, 8·5%). The *picrate* separated from ethanol in yellow plates, m. p. 119—120° (decomp.) (Found: C, 50·4; H, 4·7. $C_{11}H_{15}ON,C_6H_3O_7N_3$ requires C, 50·25; H, 4·4%). The *phenylhydrazone picrate* separated from ethanol in glistening, orange needles, m. p. 178° (decomp.) (Found: C, 56·0; H, 4·8. $C_{17}H_{21}N_3,C_6H_3O_7N_3$ requires C, 55·65; H, 4·7%).

3-Ethyl-2-(5-ethyl-2-pyridyl)indole (I; R = H).—The above ketone (0·438 g.) and freshly distilled phenylhydrazine (0·302 g.) were heated together in a vacuum on the steam-bath for 30 min. The residual mass was dissolved in anhydrous ethanol (20 ml.), cooled in ice, and saturated with dry hydrogen chloride. The solution was kept at room temperature for 1 hr. and refluxed for 2 hr.; ammonium chloride separated and after the whole had been cooled to 0° this was filtered off. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in water, basified with saturated potassium carbonate solution, and extracted with ether. The extract was dried (K_2CO_3), the solvent removed, and the indole (0·2 g.) distilled as a pale yellow, very viscous oil, b. p. (bath-temp.) 160—170°/0·2 mm., which darkened in air. The *hydrochloride* crystallised from methanol in yellow needles, softening at 149°, completely melted by 183° (Found: C, 67·25; H, 7·2. $C_{17}H_{18}N_2,HCl,H_2O$ requires C, 67·0; H, 6·9%). Light absorption: max. at 2380 and 3250 Å (log ε 4·14 and 4·16 respectively), min. at 2330 and 2765 Å (log ε 4·10 and 2·33 respectively). The *picrate* separated from ethanol in small yellow needles, m. p. 177° (decomp.) (Found: C, 57·7; H, 4·7; N, 14·4. $C_{17}H_{18}N_2,C_6H_3O_7N_3$ requires C, 57·6; H, 4·4; N, 14·6%). The *styphnate* formed yellow needles (from ethanol), m. p. 190—191° (Found: C, 55·85; H, 4·6; N, 14·2. $C_{17}H_{18}N_2,C_6H_3O_8N_3$ requires C, 55·8; H, 4·2; N, 14·1%).

Derivatives of De-ethylalstyrine of Natural Origin.—The crude picrate (1 g.) of de-ethylalstyrine was refluxed with potassium hydroxide (0·85 g.) in methanol (15 ml.) for 2 hr. The solution was filtered into a saturated sodium chloride solution (130 ml.). The solution was extracted with ether, the extract was dried (Na_2SO_4), and the ether removed, leaving an oily residue. The picrate separated from acetone or ethanol in yellow crystals, m. p. 177° not depressed on admixture with the synthetic picrate (Found: C, 57·9; H, 4·6%) (Janot and Goutarel, *loc. cit.*, report m. p. 151—152°). The styphnate separated from ethanol in yellow crystals, m. p. 188—189° not depressed on admixture with the synthetic styphnate (Found: C, 55·8; H, 4·4%). The hydrochloride as supplied to us softened at 148° and melted completely by 181° (Janot and Goutarel, *loc. cit.*, report m. p. 148—150°).

Thanks are offered to Professor M.-M. Janot for supplying samples of 5-ethylpyridine-2-carboxylic acid and the hydrochloride and crude picrate of de-ethylalstyrine of natural origin, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. M. A.).

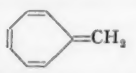
KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, May 6th*, 1954.]

Some cyclo*Heptatriene Derivatives.*

By J. H. P. VAN AARDT.

[Reprint Order No. 4103.]

ATTEMPTS to prepare heptafulvenes, such as (I), from *cyclo*heptatriene derivatives, failed. In one attempt the dehydration of a *cyclo*heptatriene alcohol (II; R = CH_2·OH) was investigated. With phosphoric oxide only polymers were formed. However, passage over alumina at 350° and fractional distillation and chromatography of the green product afforded 4-phenylstyrene, a straw-coloured liquid ($C_{14}H_{14}$), a green polymeric hydrocarbon and a dark blue azulene-like hydrocarbon.

(I)  (II)

Similar products, except for 4-phenylstyrene, were also formed when the alcohol was heated with a palladium–charcoal catalyst. The $C_{14}H_{14}$ hydrocarbon had an absorption spectrum identical with that of the alcohol from which it was derived, and it is therefore concluded that it is a methylphenyl*cyclo*heptatriene (II; R = Me), formed by disproportionation. The green viscous hydrocarbon had analytical figures corresponding to $C_{28}H_{24}$. The blue substance, in addition to its solubility in 85% phosphoric acid, was distinguished by an absorption spectrum similar to that of 1 : 2-benzazulene (Nunn and Rapson, *J.*, 1949, 825). It was formed in very small amount only.

Another unsuccessful approach was through ethyl benzyl*cyclo*heptatrienecarboxylate, which was brominated with *N*-bromosuccinimide. The product was dehydrobrominated with quinoline but no characterisable products were isolated.

In a third series of experiments, a methoxymethyl ester formed by esterification of the product of interaction of diazoacetic ester with diphenylmethyl acetate was treated with phosphoric oxide in benzene, yielding methyl stilbene-4-carboxylate as the only characterisable product.

It would appear that the heptafulvene system is not readily obtained by elimination reactions, as long as the seven-membered ring is unprotected against competing rearrangement reactions.

*Experimental.—Phenyl*cyclo*heptatrienecarboxylic acid.* Diazoacetic ester (10 g.) was added dropwise with constant stirring to diphenyl (100 g.) at 120—130°. When addition was complete the temperature was raised to 160° during 2 hr. A hot alcoholic solution of the mixture was cooled, whereupon most of the excess of diphenyl crystallised out and was filtered off. Alcoholic potash was added to the filtrate, and the acidic crystalline product (6 g.) was separated in the usual way and crystallised from aqueous alcohol, forming slightly yellow plates, m. p. 155·5° (Found: C, 79·2; H, 5·7. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%). Absorption spectrum: $\lambda_{max.}$ 236, 315 mμ; log ε 4·15, 3·98. On oxidation with aqueous potassium permanganate the acid yielded benzoic acid.

*Phenyl*cyclo*heptatrienylmethanol.* Ethyl phenyl*cyclo*heptatrienecarboxylate (10 g.) was added dropwise with vigorous stirring to a solution of lithium aluminium hydride (1 g.) in ether (30 c.c.). At the end of the addition the excess of hydride was decomposed with a little water, and the reaction mixture was poured into water, and 10% sulphuric acid added. The ethereal solution was washed with water, and the ether removed. The yellow oily residue was treated with sodium hydroxide in alcohol and water to remove unchanged ester, and the neutral fraction distilled in *vacuo*, yielding a slightly yellow oil (8 g.), b. p. 140°/0·25 mm. (Found: C, 84·7; H, 7·4%; H_2 absorbed in presence of Pd–$CaCO_3$ catalyst, 3·0 mol. Calc. for $C_{14}H_{14}O$: C, 84·8; H, 7·1%). Absorption spectrum: $\lambda_{max.}$ 299, 236 mμ; log ε 3·94, 4·19.

*Dehydration of phenyl*cyclo*heptatrienylmethanol.* (*a*) Over aluminia at 350°; (*b*) in presence of palladium–charcoal catalyst. These experiments yielded as main fraction a pale yellow liquid, b. p. *ca.* 92°/0·5 mm. (Found: C, 92·3; H, 7·7%; H_2 absorbed in presence of Pd–$CaCO_3$ catalyst, 3 mol. Calc. for $C_{14}H_{14}$: C, 92·3; H, 7·7%). The absorption spectrum of this substance was identical with that of the original carbinol.

Ethyl benzylcycloheptatrienecarboxylate. Diphenylmethane (100 g.) was treated with diazoacetic ester (10 g.) as described above for the reaction with diphenyl. The acidic product could not be crystallised and was therefore re-esterified and the ester purified by distillation. It distilled as a viscous yellow oil, b. p. 156°/1·5 mm. (Found: C, 80·0; H, 7·3%; sap. equiv., 254. Calc. for $C_{17}H_{18}O_2$: C, 80·3; H, 7·1%; sap. equiv., 254). Absorption spectrum: $\lambda_{max.}$ 285 mμ; log ε 3·65.

Microanalyses were by Mr. E. Schöning.

The author thanks Dr. W. S. Rapson, Dr. D. H. S. Horn, and Dr. D. A. Sutton for advice and assistance. This note is published with the permission of the South African Council for Scientific and Industrial Research.

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Butadienes and Related Compounds. Part II. Factors affecting the Conversion of Asymmetric Di-*p*-substituted Phenylethylenes on Bromination into 1 : 1 : 4 : 4-Tetra-arylbuta-1 : 3-dienes.*

By Wadie Tadros.

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The induction period (Tadros and Aziz, Part I *) which precedes formation of 1 : 1 : 4 : 4-tetra-*p*-alkoxyphenylbuta-1 : 3-diene from the ethylene and vinyl bromide in boiling acetic acid varied (see Table) with the amount of water present in the solvent. Now free-radical formation would be favoured by solvents of low dielectric constant (Waters, "The Chemistry of free Radicals," Clarendon Press, Oxford, 1946, p. 16): dilution of acetic acid by addition of water or absorption of atmospheric humidity increases the dielectric constant. When the crude product from the bromination of the ethylene in chloroform or carbon tetrachloride is crystallised from boiling acetic acid, the butadiene is obtained, but this is due solely to the acetic acid. Nevertheless when the bromination mixture or the mixture of the ethylene and vinyl bromide in carbon tetrachloride saturated with hydrogen bromide was left at room temperature for several days, the butadiene was slowly formed (the *p-iso*propoxy-compound was not dealkylated in such experiments at room temperature; cf. Tadros and Aziz, *loc. cit.*). The vinyl bromides, when kept in the dark in acetic acid at room temperature for 18 months, were recovered unchanged; but when exposed to direct sunlight in acetic acid or carbon tetrachloride, in presence or absence of hydrogen bromide, they were oxidised to the benzophenones; a small amount of the butadiene was formed (probably during the night) when acetic acid was the solvent. However, the butadienes were readily formed in acetic acid (Tadros and Akhnookh, unpublished work) in direct sunlight when oxygen was excluded (comment on this finding and related experiments is postponed).

Addition of pyridine to a solution of the ethylene and the vinyl bromide in glacial acetic acid prevented reaction. Whereas the replacement of the alkoxy-compound by the *p*-dimethylamino-ethylene gave the butadiene on bromination in chloroform or carbon tetrachloride, the *p*-chloro-compound did not, even in boiling acetic acid. 1 : 1 : 4 : 4-Tetra-*p*-chlorophenylbuta-1 : 3-diene (Brand *et al.*, *J. pr. Chem.*, 1930, **127**, 219, 240) was obtained (together with other products) only when the crude product was heated at 280—300°. The structures of the *p*-chloro-butadiene and of 1 : 1-di-*p*-methoxyphenyl-4 : 4-di-*p-iso*propoxyphenylbuta-1 : 3-diene, which could be readily obtained, were confirmed by ozonolysis. The effect of hydrogen bromide on the formation of the butadienes has been emphasised (see Table).

* Part I, *J.*, 1951, 2553.

1 : 1-Di-*p*-benzyloxyphenylethanol was obtained—in larger proportions in large-scale experiments—on decomposition of the product from methylmagnesium iodide and 4 : 4′-dibenzyloxybenzophenone with cold aqueous ammonium chloride solution.

Experimental.—**1 : 1-*Di*-p-*methoxyphenyl*-4 : 4-*di*-p-iso*propoxyphenylbuta*-1 : 3-*diene*.** A solution of 1 : 1-di-*p*-*iso*propoxyphenylethylene (0·592 g.) and di-*p*-methoxyphenylvinyl bromide (0·64 g., 1 mol.) in glacial acetic acid (10 c.c.) was boiled for 2 min. The *butadiene* (0·9 g.; sinters at 150°, m. p. 175°) separated on cooling and, crystallised from acetic acid, was pale greenish-yellow (m. p. 155°; 0·75 g.) (Found: C, 80·2; H, 7·3. $C_{36}H_{38}O_4$ requires C, 80·9; H, 7·1%). On dilution of the acetic acid mother-liquor and fractional crystallisation of the precipitate from little acetic acid, 1 : 1 : 4 : 4-tetra-*p*-methoxy-, m. p. 204—205°, and 1 : 1 : 4 : 4-tetra-*p*-*iso*propoxy-phenylbuta-1 : 3-diene, m. p. 187°, showing no depression on admixture with authentic samples, were obtained. The possibility that the product of m. p. 155° was a mixture of these two butadienes was eliminated as follows: m. p.s of a mixture of the tetramethoxy- and the tetra*iso*propoxy-diene softened at 180° and melted at 195°; one of the tetramethoxy-diene and the diene of m. p. 155° softened at 155° and melted at 190°; one of the tetra*iso*propoxy-diene and the diene of m. p. 155° softened at 155° and melted at 165°.

1 : 1 : 4 : 4-*Tetra*-p-*chlorophenylbuta*-1 : 3-*diene*. A solution of bromine (6·4 g.) in carbon tetrachloride (10 c.c.) was added to one of 1 : 1-di-*p*-chlorophenylethylene (10 g.) (Grummit, Buck, and Becker, *J. Amer. Chem. Soc.*, 1945, **67**, 2265) in the same solvent (50 c.c.). The solvent was removed and the residue was heated at 280—300° for 15 min. The dark brown material thus obtained was triturated with acetone, a brown residue (m. p. above 320°) being undissolved. The acetone solution was filtered and solvent removed. The residue of *diene* crystallised from ethyl acetate as brownish-yellow crystals, m. p. 244° (1 g.) (Found: C, 67·3; H, 4·1; Cl, 28·2. Calc. for $C_{28}H_{18}Cl_4$: C, 67·7; H, 3·6; Cl, 28·6%).

Experiment	Solvent	Temp.	Induction period	R in *p*-subst. OR	Butadiene G.
I	99% AcOH	B. p.	2 min.	Me	0·75
	90% AcOH	B. p.	5–6 min.	Me	0·80
	80% AcOH	B. p.	15–20 min.	Me	0·25 (after 0·5 hr.)
	80% AcOH *	B. p.	1 min.	Me	0·25 (after 20 min.)
			Reaction period		
	CCl_4	B. p.	6 hr.	Me	0
	CCl_4 *	B. p.	6 hr.	Me	0·1
	99% AcOH or CCl_4	20—25°	25 days	Me or Et	0
	99% AcOH *	,,	,,	Me	0·85
				Et	0·95
	CCl_4 *	,,	,,	Me or Et	0·3
II	99% AcOH	,,	18 months	Me or Et	0
	99% AcOH *	,,	25 days	Me or Et	0·06
III	99% AcOH	,,	,,	Me, Et, or Pr^i	*ca.* 0·85
	CCl_4	,,	,,	Me or Et	0·3
				Pr^i	0·08
	CCl_4 †	B. p.	2 hr.	Me or Et	0

* Solvents saturated with HBr.

I. 1 : 1-Di-*p*-methoxy- (0·48 g., 1 mol.) or -ethoxy-phenylethylene (0·536 g., 1 mol.) and the corresponding vinyl bromide (methoxy-, 0·64 g.; ethoxy-, 0·694 g., 1 mol.), solvent (10 c.c.). With 80% AcOH, the mother-liquor was yellow, otherwise it was dark olive-green.

II. A solution of the di-*p*-alkoxyphenylvinyl bromide (0·5 g.) in the solvent (10 c.c.) was left in the dark. The solutions saturated with hydrogen bromide became rose within 24 hr., gradually changing to wine-red and then brown.

III. A solution of bromine (0·3 g.) in the solvent (2 c.c.) was added to one of the ethylene in the same solvent (8 c.c.). In these experiments the *iso*propoxy-compound did not undergo cleavage.

† A mixture of the ethylene and the corresponding vinyl bromide only (methoxy-, m. p. 84°; ethoxy-, m.p. 64°) was obtained.

The butadienes had m. p. and mixed m. p.: R = Me, 204—205°; Et, 207°; Pr^i, 187°.

1 : 1 : 4 : 4-*Tetra*-p-*dimethylaminophenylbuta*-1 : 3-*diene*. A solution of bromine (0·9 g.) in chloroform or carbon tetrachloride (2 c.c.) was added to one of 1 : 1-bis-*p*-dimethylaminophenylethylene (1·5 g.) (Freund and Mayer, *Ber.*, 1906, **39**, 1117) in the same solvent (12 c.c.). The solvent was removed, the residue was treated with a few c.c. of 3% aqueous sodium hydroxide, filtered off, washed with water, and treated with boiling alcohol, and the undissolved *butadiene* crystallised from acetone as brownish- or greenish-yellow crystals which softened at 274° and

melted at 282° (0·2 g.) (Found : C, 81·2; H, 7·7; N, 10·9. $C_{36}H_{42}N_4$ requires C, 81·5; H, 7·9; N, 10·6%).

1 : 1-*Di*-p-*benzyloxyphenylethanol.* 4 : 4′-Di-*p*-benzyloxybenzophenone (100 g.) was added to methylmagnesium iodide (from magnesium, 9·1 g., and methyl iodide, 54 g.) in ether (500 c.c.) with stirring, during 2 hr., and then left overnight. The mixture was decomposed with cold aqueous ammonium chloride and extracted with ether or benzene–ether. The *alcohol* crystallised from ethanol as colourless crystals, m. p. 87° (70 g.) (Found : C, 82·5; H, 6·0. $C_{35}H_{36}O_3$ requires C, 82·0; H, 6·3%).

Effect of sunlight on the alkoxy-vinyl bromides. On exposure to direct sunlight of a solution of di-*p*-methoxy(or -ethoxy)phenylvinyl bromide (0·5 g.) in acetic or carbon tetrachloride (10 c.c.) in a silica flask, the vinyl compound was oxidised to 4 : 4′-dimethoxy- (m. p. and mixed m. p. 142°) and 4 : 4′-diethoxy-benzophenone (m. p. and mixed m. p. 127°). The solution became successively yellow, wine-red, brown-red, and finally yellow (within 4—6 weeks depending on season of exposure) when the reaction was almost complete.

Ozonolysis. The butadienes (see Tadros and Aziz, *loc. cit.*) gave glyoxal, identified as its bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 318°, and the corresponding ketone. The *p*-chloro-butadiene gave 4 : 4′-dichlorobenzophenone, m. p. and mixed m. p. 144°. 1 : 1-Di-*p*-methoxyphenyl-4 : 4-di-*p*-*iso*propoxyphenylbuta-1 : 3-diene gave 4 : 4′-dimethoxy-, m. p. and mixed m. p. 142°, and 4 : 4′-di*iso*propoxybenzophenone, m. p. and mixed m. p. 72°, separated by fractional crystallisation from dilute alcohol.

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Tetrazolium Compounds. Part IV. C-Heterocyclic Derivatives.*

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IN Parts II and III * of this series, formazans and tetrazolium salts bearing phenylazophenyl and styrylphenyl substituents were described. The present note deals with similar compounds in which a heterocyclic ring is attached to the carbon atom of the formazan chain or tetrazole nucleus.

The pyridine derivatives were prepared mainly to assess their potentialities as antitubercular agents since the 3-pyridylformazans and 5-pyridyltetrazolium salts have structural features in common with pyridine-4-carboxyhydrazide (" Isoniazid ").

Experimental.—The formazans (see Table 1) were prepared by the methods indicated in Part I (*J.*, 1953, 3881). Those carrying quaternary pyridine substituents were obtained by direct quaternisation of the simple pyridylformazans with methyl chloride, iodide, or sulphate in methanol.

Oxidations were effected with yellow mercuric oxide in methanol, and tetrazolium compounds (Table 2) were usually isolated as halides. The tetrazolium chloride from 1 : 5-diphenyl-3-4′-pyridylformazan was not obtained pure and was converted into the di(hydrogen sulphate) by treatment with methanolic sulphuric acid. 3-2′-Furyl-1 : 5-diphenylformazan is new but the corresponding tetrazolium chloride has been mentioned (Mattson, Jensen, and Dutcher, *Science*, 1947, **106**, 294; Bielig and Querner, *Z. Naturforsch.*, 1949, **4**b, 21) without details. This formazan was purified by chromatography on alumina.

4-Formyl-2-phenyl-2 : 1 : 3-triazole (Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 735) gave the *phenylhydrazone*, pale yellow needles (from ethanol), m. p. 117° (Found : C, 68·4; H, 5·0; N, 26·6. $C_{15}H_{13}N_5$ requires C, 68·5; H, 5·0; N, 26·6%).

* Parts II and III, *J.*, 1954, 1565, 1568.

TABLE 1. *Formazans*, Ph·NH·N:CR′·N:N·C_6H_4R-*p*.

No.	R	R′	Yield (%)	M. p.	Appearance	Solvent
1	H	4-Pyridyl	46	185—187°	Red plates, golden reflex	$MeNO_2$
2	OMe	,,	95	158	Red needles, blue reflex	*cyclo*Hexane
3	Cl	,,	40	170—172	Red plates, golden reflex	$MeNO_2$
4	N:NPh	,,	39	194	Red needles, green reflex	Dioxan–H_2O
5	CH:CHPh	,,	40	184—187	,, ,,	,,
6*a*	H	4-*N*-Methylpyridinium chloride	80	210—212	,, ,,	H_2O
6*b*	H	4-*N*-Methylpyridinium iodide	92	233—234 †	,, ,,	$MeNO_2$
6*c*	H	4-*N*-Methylpyridinium methyl sulphate	81	204—205	Red needles, blue reflex	EtOH
7	CH:CHPh	4-*N*-Methylpyridinium iodide	84	200 †	,, ,,	$MeNO_2$
8	H	2-Furyl	14	118	Purple prisms, golden reflex	Light petroleum (b. p. 80—100°)
9	H	2-Phenyl-2 : 1 : 3-triazol-4-yl	59	163—164	Red needles, golden reflex	$MeNO_2$

† With decomp.

No.	Formula	Found (%) C	H	N	Hal.	Required (%) C	H	N	Hal.
1	$C_{18}H_{15}N_5$	71·3	5·25	23·5	—	71·8	5·0	23·3	—
2	$C_{19}H_{17}ON_5$	69·5	5·05	21·2	—	68·9	5·2	21·1	—
3	$C_{18}H_{14}N_5Cl$	—	—	21·0	10·8	—	—	20·9	10·6
4	$C_{24}H_{19}N_7$	—	—	23·7	—	—	—	24·2	—
5	$C_{26}H_{21}N_5$	—	—	17·2	—	—	—	17·4	—
6*a*	$C_{19}H_{18}N_5Cl$	—	—	19·2	10·0	—	—	19·9	10·1
6*b*	$C_{19}H_{18}N_5I$	—	—	16·7	29·1	—	—	15·8	28·7
6*c*	$C_{20}H_{21}O_4N_5S$ ‡	—	—	16·55	—	—	—	16·4	—
7	$C_{27}H_{24}N_5I$	—	—	12·6	23·2	—	—	12·8	23·3
8	$C_{17}H_{14}ON_4$	70·6	4·95	19·35	—	70·3	4·9	19·3	—
9	$C_{21}H_{17}N_7$	68·9	4·9	26·9	—	68·7	4·7	26·7	—

‡ Found : S, 7·8. Reqd. : S, 7·5%.

TABLE 2. *Tetrazolium salts*, *p*-R·C_6H_4·N=N(Ph·N—N)C·R′

No.*	Anion	Yield (%)	M. p.	Appearance	Solvent	Formula	Found (%) N	Hal	Reqd. (%) N	Hal
1	I [a]	47	226—227° †	Orange needles	EtOH	$C_{18}H_{14}N_5I$	16·2	30·1	16·4	29·8
2	Cl	58	157—160	Yellow needles	PrⁱOH	$C_{19}H_{16}ON_5Cl,HCl,2H_2O$	16·05	16·0	16·0	16·2
4	Br	32	178—180 (sinters at 158)	Scarlet prisms	H_2O	$C_{24}H_{18}N_7Br,H_2O$	19·7	15·9	19·5	15·9
5	Cl	51	213—216 †	Yellow prisms	,,	$C_{26}H_{20}N_5Cl,H_2O$	15·6	7·9	15·4	7·8
6	HSO_4 [b]	5	158—160	Pale yellow prisms	Dry EtOH	$C_{19}H_{19}O_8N_5S_2$ ‡	14·1	—	13·8	—
8	Cl	51	239—240	Pale yellow prisms	EtOH–Et_2O	$C_{17}H_{13}ON_4Cl$	17·1	11·0	17·2	10·9
9	Cl	40	253—254 †	Colourless needles	,,	$C_{21}H_{16}N_7Cl$	24·3	9·0	24·4	8·8

[a] The bromide has been described by Kuhn and Münzing (*Chem. Ber.*, 1953, **86**, 858). [b] The anion on the *N*-methylpyridinium moiety is also HSO_4.

* The tetrazolium salts have the R and R′ of the formazans of corresponding number in Table 1.

† With decomp. ‡ Found : S, 12·3. Reqd. : S, 12·6%.

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The Infra-red Spectrum of Dideuteroglyoxal.

By J. C. D. Brand and G. J. Minkoff.

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Electron-diffraction experiments (LuValle and Shomaker, *J. Amer. Chem. Soc.*, 1939, **61**, 3520) and the fine structure of certain infra-red bands (Cole and Thompson, *Proc. Roy. Soc.*, 1949, *A*, **200**, 10) have been interpreted in favour of the centrosymmetrical planar form of glyoxal (point-group, C_{2h}) as the configuration of lowest energy. The representation of the fundamentals is therefore $\Gamma = 5A_g + 2A_u + B_g + 4B_u$, six fundamentals being active in the infra-red and six in the Raman spectrum with mutual exclusion on account of the centre of symmetry. Cole and Thompson have assigned unequivocally four of the infra-red active fundamentals of normal glyoxal, and the remaining two almost certainly lie in the unmapped region beyond 15 μ. Because of experimental difficulties the Raman spectrum has not been measured, but the majority of the Raman-active fundamentals can be found in the ultra-violet spectrum (Thompson, *Trans. Faraday Soc.*, 1940, **36**, 988; Gaydon, *ibid.*, 1947, **43**, 36; Brand, *ibid.*, 1954, **50**, 431) and frequencies are listed in the Table for both normal and isotopic glyoxal where the assignment is believed to be certain or very probable.

Fundamental vibrational frequencies of glyoxal and dideuteroglyoxal.

				$C_2H_2O_2$	$C_2D_2O_2$	$\pi(\nu^1/\nu)^2$
A_g	R	CH, stretching	ν_1	2809	—	—
		CO, stretching	ν_2	1742	1722	—
		CHO, deformation	ν_3	—	—	—
		CC, stretching	ν_4	1201	—	—
		CHO, rocking	ν_5	553	537	—
A_u	IR	CH, wagging	ν_6	801·5 *	~630	—
		Torsional	ν_7	127	117	0·53 (calc., 0·52)
B_g	R	CH, wagging	ν_8	1048	911	0·76 (calc., 0·76)
B_u	IR	CH, stretching	ν_9	2836·2 *	2141	—
		CO, stretching	ν_{10}	1739	1712	—
		CHO, deformation	ν_{11}	1311·5 *	1008	—
		CHO, rocking	ν_{12}	—	—	—

Values marked * are from high-dispersion measurements by Cole and Thompson (*loc. cit.*). The A_g and B_g fundamental frequencies and the torsional frequency are taken from the ultra-violet spectrum. All measurements refer to the vapour.

Between 3 and 25 μ dideuteroglyoxal has only three regions of strong absorption (at 2141, 1712, and 1008 cm.$^{-1}$) which are clearly the B_u fundamentals ν_9, ν_{10}, and ν_{11}. At 1008 cm.$^{-1}$ the profile is of a type B band with maxima 8 cm.$^{-1}$ on either side of a central gap (cf. 10 cm.$^{-1}$ for normal glyoxal); the fact that the band is of type B is curious and the vibration must be a CHO planar deformation rather than a simple C–H rocking mode (type A). Of the remaining three infra-red-active fundamentals, the torsional mode certainly lies outside the region examined and the frequency in the Table is taken from the ultra-violet spectrum. The fundamental $\nu_6(A_u)$ was not visible with the available path of 0·3 cm.-at. of dideuteroglyoxal, and the frequency of ~630 cm.$^{-1}$ was calculated from the product rule. The missing B_u fundamental, ν_{12}, is quite uncertain: no absorption was found in the region 15—25 μ with a moderately long path (1 cm.-at.) of normal glyoxal but this might be due to low intensity and does not prove that the frequency lies below 400 cm.$^{-1}$; however it is noteworthy that the corresponding fundamental of buta-1 : 3-diene has been assigned provisionally at 320 cm.$^{-1}$ (Richards and Nielsen, *J. Opt. Soc. Amer.*, 1950, **40**, 438).

The assignment of the fundamentals in the present paper differs materially from that given by Thompson and by Gaydon (*locc. cit.*). The moments of inertia required for the product rule ratios, calculated from the electron-diffraction parameters, are:

$$\left.\begin{array}{ll} \text{for} & C_2H_2O_2: I_a = 8{\cdot}52,\ I_b = 103{\cdot}7 \text{ a.w.-Å}^2 \\ \text{for} & C_2D_2O_2: I_a = 12{\cdot}83,\ I_b = 104{\cdot}4 \end{array}\right\} \text{and } I_c = I_a + I_b$$

With the possible exception of the carbonyl frequencies it is clear that the A_g and B_g fundamentals do not appear in the infra-red, and the vibrational evidence for a centre of symmetry can be regarded as definite. Evidence for a plane of symmetry in addition to a centre, and hence for the species classification used in this paper, rests mainly on the electron-diffraction measurement. The spectroscopic evidence on this point is inconclusive, for the I_a's of the planar model and of the alternative (but structurally less plausible) centrosymmetrical non-planar configuration (S_2) are very similar and the fine structure of the infra-red bands is insensitive to deformation of the molecular plane.

Experimental.—Infra-red spectra were recorded with a double-beam spectrometer (Minkoff, *Fuel*, 1950, **3**, 221) with sodium chloride and potassium bromide optics. Dideuteroglyoxal was synthesised by mercury-photosensitised combination of deuterium and carbon monoxide.

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The Kinetics of Oxidation of Benzaldehyde. Part III. Note on the Reaction Catalysed by Benzoyl Peroxide.*

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THE formation of hydroperoxide from liquid olefins and oxygen has been shown by Bolland and Gee and their collaborators (Bolland, *Quart. Reviews*, 1949, **3**, 1) to occur by the following mechanism :

Initiation	$\longrightarrow$ R· or RO_2· . . . (1)	$R\cdot + R\cdot \longrightarrow$	Termination	.	(4)
$R\cdot + O_2 \longrightarrow$	$RO_2\cdot$ . . . . . (2)	$R\cdot + RO_2\cdot \longrightarrow$		.	(5)
$RO_2\cdot + RH \longrightarrow$	ROOH + R· . . . (3)	$RO_2\cdot + RO_2\cdot \longrightarrow$		.	(6)

At sufficiently high oxygen concentration termination occurs by reaction (6) and the rate is given by :

$$\rho \equiv -\mathrm{d}[O_2]/\mathrm{d}t = k_3 (R_i/k_6)^{\frac{1}{2}}[RH] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

where R_i is the rate of initiation. The kinetics of the oxidation of aldehydes differ in some respects from those of olefins, but Bowen and Tietz (*J.*, 1930, 234), Cooper and Melville (*J.*, 1951, 1984, 1994), Fillet, Niclause, and Letort (*Compt. rend.*, 1953, **236**, 1489), and Ingles and Melville (*Proc. Roy. Soc., A*, 1953, **218**, 175) have shown that the kinetics of the photochemically initiated reaction conform to the requirements of equation (*A*). The experiments reported here were carried out to test the validity of equation (*A*) for the oxidation of benzaldehyde catalysed by benzoyl peroxide. The equation requires that at "high" oxygen concentrations the rate should be (*a*) proportional to $[Bz_2O_2]^{\frac{1}{2}}$, (*b*) proportional to [Ph·CHO], and (*c*) independent of $[O_2]$. Previous work (Part I) has shown that requirement (*a*) is fulfilled. However, the present experiments have been extended over a somewhat greater temperature range. The reaction was carried out in benzene solution, apparatus, experimental procedure, and methods of purification of reagents being as described in Part I.

Results.—(*a*) Fig. 1 shows the dependence of ρ on $[Bz_2O_2]^{\frac{1}{2}}$ at 4 temperatures. Each curve is linear over the whole range of peroxide concentration. As pointed out in Part I * this indicates that termination of the catalysed reaction occurs by mutual interaction of the chain-carriers, and that the rates of the catalysed reaction, ρ_c, and of the residual uncatalysed reaction, ρ_u, are

* Parts I and II, *Proc. Roy. Soc.*, 1953, *A*, **216**, 10, 30.

additive. Thus, the total rate of oxidation in the presence of added peroxide is given by $\rho_t = \rho_c + \rho_u$, where $\rho_c \propto [Bz_2O_2]^{\frac{1}{2}}$. The activation energy for ρ_c may be derived from an Arrhenius plot of the slopes (obtained by the method of least squares) of the lines in Fig. 1 (see Fig. 2, curve *A*). Thus $E_c = 17{\cdot}2$ kcal./mole. Fig. 2 also shows (curve *B*) a plot of $\log_{10} \rho_u$ against $1/T$; this gives **13·6** kcal. for the apparent activation energy of the thermal reaction under these conditions.

(*b*) Values of ρ_c obtained at several concentrations of benzaldehyde with constant oxygen pressure and $[Bz_2O_2]$ are given in Table 1. ρ_c (penultimate column) was obtained by subtracting ρ_u from ρ_t and correcting the result ($^1\rho_c$) for the small variations in $[Bz_2O_2]$ which resulted from the method of preparation of the solution. The constancy of $\rho_c/[Ph{\cdot}CHO]$ (last column)

FIG. 1. *Variation of rate of oxygen absorption with square root of benzoyl peroxide concentration. Oxygen pressure = 523 mm.; benzaldehyde = 0·224 mole fraction in benzene.*

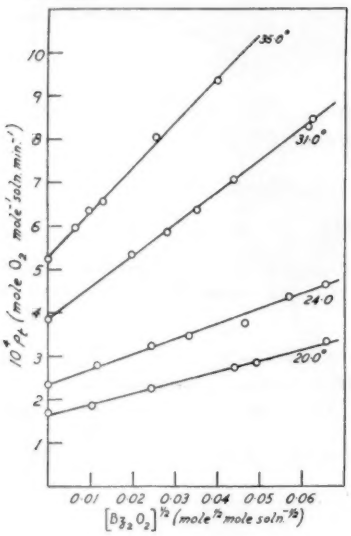

FIG. 2. *Dependence on temperature of (A) slope of ρ_c–$[Bz_2O_2]^{\frac{1}{2}}$ relationship and of (B) ρ_u.*

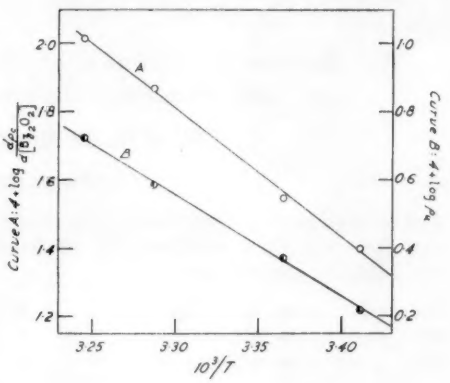

TABLE 1. *Values of ρ_t, ρ_u, and ρ_c at various benzaldehyde concentrations.*

Oxygen pressure = 523 mm.; $[Bz_2O_2] = 2{\cdot}95 \times 10^{-3}$ mole/mole soln.; $T = 31{\cdot}0°$.†

Ph·CHO, mole fraction	ρ_t	ρ_u	$^1\rho_c = \rho_t - \rho_u$	ρ_c	$10^3\rho_c/[Ph{\cdot}CHO]$
		10^4 (mole O_2/mole soln. min.) †			
0·0446	0·88	0·05	0·83	0·84	1·88
0·0878	2·30	0·61	1·69	1·69	1·92
0·133	3·83	1·24	2·59	2·59	1·95
0·179	5·96	2·62	3·34	3·33	1·86
0·224	7·79	3·80	3·99	3·96	1·77

† In these units soln. means benzaldehyde + benzene.

within the experimental error shows that the dependence of ρ_c on [Ph·CHO] is linear over the range of [Ph·CHO] allowed by the experimental conditions.

(*c*) Values of ρ_c obtained at different oxygen pressures and constant concentrations of aldehyde and peroxide are given in Table 2 (last column).

The results show that over the range of oxygen concentration corresponding to the pressure range indicated, ρ_c is substantially independent of $[O_2]$.

TABLE 2. *Values of* ρ_t, ρ_u, *and* ρ_c *at various oxygen pressures.*

P_{O_2}, mm.	ρ_t	ρ_u *	$\rho_c = \rho_t - \rho_u$
	10^4 (mole O_2/mole soln. min.) †		
(i) Mole fraction Ph·CHO = 0·133; $[Bz_2O_2] = 2{\cdot}95 \times 10^{-3}$ mole/mole soln.; $T = 31{\cdot}0°$.†			
579	3·87	1·21	2·66
522	3·83	1·24	2·59
417	3·65	1·30	2·35
338	3·78	1·33	2·45
(ii) Mole fraction Ph·CHO = 0·045; $[Bz_2O_2] = 11{\cdot}08 \times 10^{-3}$ mole/mole soln.; $T = 31{\cdot}0°$.†			
497	2·26	0·05	2·21
271	2·46	0·07	2·39
105	2·37	0·13	2·24

* Interpolated values (Mulcahy and Watt, *loc. cit.*).
† In these units soln. means benzaldehyde + benzene.

Discussion.—The results are in agreement with expectation based on the mechanism proposed by Bolland and Gee, which therefore may be considered to apply to the peroxide-catalysed oxidation (at high concentrations of oxygen). From equation (*A*) it follows that $E_c = \frac{1}{2}E_1 + E_3 - \frac{1}{2}E_6 = 17{\cdot}2$ kcal.*

E_1 may be equated to the dissociation energy of the O–O bond in benzoyl peroxide. Setting $E_1 = 29{\cdot}8$ kcal./mole (Swain, Stockmayer, and Clarke, *J. Amer. Chem. Soc.*, 1950, **72**, 5426; Bawn and Mellish, *Trans. Faraday Soc.*, 1951, **47**, 1216) and $\frac{1}{2}E_6 \simeq 0$ (Bolland, *Trans. Faraday Soc.*, 1950, **46**, 358; Ingles and Melville, *loc. cit.*), we obtain $E_3 = 2{\cdot}3$ kcal. This agrees within experimental error with the value $E_3 = 1{\cdot}8$ kcal. derived from the photoinitiated reaction (in *n*-decane solution) by Ingles and Melville. It is noteworthy that the value of E_3 for benzaldehyde is smaller than the corresponding value obtained with any of the fifteen olefinic compounds studied by Bolland (*loc. cit.*).

By setting R_i equal to twice the rate of dissociation of benzoyl peroxide ($R_{O\text{–}O}$) into radicals (Bateman and Morris, *Trans. Faraday Soc.*, 1952, **48**, 1149) the magnitude of $k_3k_6^{-\frac{1}{2}}$ may be derived from the present results and those of Bawn and Mellish (*loc. cit.*) for $R_{O\text{–}O}$ (in benzene solution). The value at 25° is given in Table 3 together with values

TABLE 3.

	Initiator	$k_3k_6^{-\frac{1}{2}}$ l.$^{\frac{1}{2}}$ mole$^{-\frac{1}{2}}$ sec.$^{-\frac{1}{2}}$	Solvent	Author
Benzaldehyde	benzoyl peroxide	0·85	benzene	Present work
Benzaldehyde	photochemical	0·16	*n*-decane	Ingles and Melville
n-Decanaldehyde	photochemical	0·7	*n*-decane	Cooper and Melville
2 : 6-Dimethylhepta-2 : 5-diene	AZDN	0·13	pure liquid	Bateman and Morris

calculated from the results of Melville *et al.* for benzaldehyde and *n*-decanaldehyde and that obtained by Bateman and Morris (*Trans. Faraday Soc.*, 1953, **49**, 1026) for 2 : 6-dimethylhepta-2 : 5-diene. Two points emerge from the Table : our value for $k_3k_6^{-\frac{1}{2}}$ does not agree with that of Melville and his collaborators for benzaldehyde (it is closer to their result for *n*-decanaldehyde) and it is about seven times greater than the corresponding value for dimethylheptadiene (cf. Bateman and Morris, *loc. cit.*). This difference between benzaldehyde and the olefins is thus in the same sense as the difference in the values of E_3. For equal rates of initiation and [RH], the chain length, ν, is proportional to $k_3k_6^{-\frac{1}{2}}$ and is therefore greater with benzaldehyde than with the olefins. Under the conditions of our experiments ν is of the order of 10^4—10^5.

Note on the Uncatalysed Reaction.—The value $E_u = 13{\cdot}6$ kcal. for the uncatalysed reaction with Ph·CHO mole fraction = 0·224 (Fig. 2) falls between the values 17·5 and 6 kcal. obtained (Part II) for "low" and "high" concentrations of benzaldehyde, respectively. Ingles and Melville using a solution of benzaldehyde of 0·32 mole fraction in *n*-decane find

* It is to be observed that the value of E_c is close to that of E_u at "high" oxygen concentrations (17·5 kcal.; cf. Part II) though the significance of the coincidence (if any) is not clear at present.

a value of 7·6 kcal. The reason for the discrepancy is at present obscure. We have found (unpublished) $E_u = 7{\cdot}7$ kcal. for pure undiluted benzaldehyde oxidizing under 617 mm. of oxygen.

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Reactions of Aromatic Nitro-compounds with Alkaline Sulphides. Part V. 2 : 3-, 2 : 6-, and 1 : 7-Dinitronaphthalenes.*

By E. R. WARD, T. M. COULSON, and J. G. HAWKINS.

[Reprint Order No. 5252.]

THE reduction with almost neutral aqueous methanolic sodium hydrogen sulphide of dinitronaphthalenes (cf. Part III, Hodgson and Ward, *J.*, 1949, 1187) has now been extended to the 2 : 3-, 2 : 6-, and 1 : 7-isomers. In each case the initial products were a nitronaphthylamine and the corresponding sodium nitronaphthyl sulphide. The yield of 3-nitro-2-naphthylamine is a considerable improvement on that obtained by van Rij, Verkade, and Wepster (*Rec. Trav. chim.*, 1951, **70**, 236) who used sodium disulphide, again emphasising the advantage of our method of selective reduction.

The percentage conversions of starting material into (*A*) nitronaphthylamine and (*B*) sodium nitronaphthyl sulphide, for the 10 dinitronaphthalenes are (cf. Part III) :

Isomer	1 : 2	1 : 3	1 : 4	2 : 3	1 : 5	1 : 6	1 : 7	1 : 8	2 : 6	2 : 7
A	0	82 *	5	69	55—58	60—62	38	0	70	80
B	100	18	95	31	45—42	40—38	62	100	30	20

* In this case a mixture of isomeric nitronaphthylamines.

Whilst we agree with Hodgson and Ward (*loc. cit.*) that the important factor is the electropositivity of the carbon atom to which the attacked nitro-group is attached, we cannot satisfactorily interpret the reactions on the basis of a quinonoid hypothesis (Vesely and Jakes, *Bull. Soc. chim.*, 1923, **33**, 955; Hodgson and Hathway, *J. Soc. Dyers and Col.*, 1945, **61**, 283). Such an hypothesis suggests that transmission of electronic effects from one nucleus to the other in naphthalene derivatives is a general phenomenon. Internuclear activation has certainly been demonstrated for both electrophilic and nucleophilic reactions but is weak compared with effects transmitted within one nucleus (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 273).

Our present results show the abnormal behaviour of 1 : 3- and 1 : 8-dinitronaphthalene, which is accentuated by detailed comparison with the reactivity of 1 : 5-dinitronaphthalene and 1 : 3 : 8-trinitronaphthalene (Hodgson and Ward, *J.*, 1945, 794; 1947, 1109) with aqueous methanolic sodium hydrogen sulphide. 1 : 3- and 1 : 8-Dinitronaphthalenes show other unusual properties (Ward, Thesis, London Univ., 1946). We consider that surveys of the reactivity of complete groups of naphthalene derivatives are necessary before satisfactory general interpretation of the reactivity of naphthalene compounds can be made.

Experimental.—The procedures followed for reduction and for isolation of products are described in Part III. Preliminary runs indicated the approximate proportions of products, and the amount of reducing agent required for complete conversion. As a further precaution reducing agent was added until a " permanent excess " was detectable in the reaction mixture. In each case the amount of reducing agent required was in reasonable agreement with that calculated from the yield of nitronaphthylamine, it being assumed that the other product was the sodium nitronaphthyl sulphide.

1 : 7-*Dinitronaphthalene.* The 8-nitro-2-naphthylamine which separated from the diluted mixture could be removed by filtration only after standing overnight. Consequently, only a small amount of bisnitronaphthyl disulphide was isolated, which could not be obtained crystalline.

* Part IV, *J.*, 1952, 398.

2 : 6-*Dinitronaphthalene*. After removal of precipitated 6-nitro-2-naphthylamine the filtrate was acidified, and the nitronaphthyl sulphide collected, redissolved in aqueous sodium hydroxide, and allowed to oxidise in the air. The *bis*-(6-*nitro*-2-*naphthyl*) *disulphide* when crystallised from hot acetic acid had m. p. 264° (decomp.) (Found : S, 15·8. $C_{20}H_{12}O_4N_2S_2$ requires S, 15·7%).

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The Nitration of β-*Nitronaphthalene.*

By E. R. WARD and J. G. HAWKINS.

[Reprint Order No. 5345.]

BY nitration of β-nitronaphthalene in acetic acid with fuming nitric acid and sulphuric acid Vesely and Jakes (*Bull. Soc. chim.*, 1923, **33**, 952) obtained a mixture of dinitronaphthalenes. From this they claimed to have separated 1 : 6- and a minute amount of 1 : 7-dinitronaphthalene by crystallisation procedures. By nitration in sulphuric acid only they obtained mixed dinitronaphthalenes and 1 : 3 : 8-trinitronaphthalene. In all cases the polynitro-compounds were identified with authentic specimens. We have re-investigated these nitrations, but like Dean (Thesis, London, 1952) we could not separate pure 1 : 6-dinitronaphthalene from the nitration products by crystallisation. However, examination of the product obtained by nitration in sulphuric acid by means of its infra-red absorption spectrum in the region 8—15 μ established the presence of 1 : 6- (42 ± 5%) and 1 : 7-dinitronaphthalene (52 ± 5%) and 1 : 3 : 8-trinitronaphthalene (9 ± 5%) (the infra-red spectra of all known polynitronaphthalenes, have been surveyed by Whiffen, Hawkins, and Ward, unpublished work). Other known trinitronaphthalenes appeared to be absent.

The product from similar nitration of α-nitronaphthalene contained 1 : 8- (69 ± 5%) and 1 : 5-dinitronaphthalene (31 ± 5%) and some trinitronaphthalenes. Fierz-David and Sponagel (*Helv. Chim. Acta*, 1943, **26**, 98) reported that nitration at −55° afforded a 78 : 22 mixture of these dinitronaphthalenes together with some 1 : 3 : 8-trinitronaphthalene.

Experimental.—α-Nitronaphthalene (2 g.; m. p. 56°) or β-nitronaphthalene (2 g.; m. p. 75·5°) was dissolved in sulphuric acid (*d*, 1·84; 16 c.c.) and treated very slowly, with vigorous stirring, with 4 : 1 (vol.) sulphuric (*d* 1·84)–nitric acid (*d* 1·42) until the dark red solution just became yellow, the temperature being kept at 0°. The mixture was poured on ice and water, and the precipitate collected, washed with much water, and dried for 36 hr. at 55°.

The infra-red spectra were measured, in Nujol mull, on a Grubb-Parsons spectrometer with a sodium chloride prism. For the quantitative estimation the nitration product obtained from α-nitronaphthalene was examined in the range 710—690 cm.$^{-1}$ and that from β-nitronaphthalene in the range 785—705 cm.$^{-1}$, with an approx. 4% solution in dioxan and a cell of thickness 0·11 mm.

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A Synthesis of (−)-β-Amino-γ-methylvaleric Acid [(−)-β-Leucine].

By K. Balenović and D. Dvornik.

[Reprint Order No. 5277.]

Inactive β-leucine has recently been prepared by Birkhofer and Storch (*Chem. Ber.*, 1953, **86**, 529) by hydrolysis of dihydro-4-*iso*propyluracil with hydrochloric acid.

By application of the Arndt–Eistert reaction to (−)-1-diazo-4-methyl-3-phthalimidopentan-2-one prepared from D-valine (cf. *Experientia*, 1947, **3**, 369), (−)-β-amino-γ-methylvaleric acid [(−)-β-leucine] has been obtained in an overall yield of 48% based on D-valine.

Experimental.—M. p.s were determined on a Kofler block.

N-Phthaloyl-D-valine chloride. *N*-Phthaloyl-D-valine (4·4 g.; $[\alpha]_D$ +68°) (Fling, Minard, and Fox, *J. Amer. Chem. Soc.*, 1947, **69**, 2466) and thionyl chloride (5 c.c.) were heated for 0·5 hr. at 60°; the excess of thionyl chloride was then removed under reduced pressure and the residual crude *N-phthaloyl-D-valine* chloride (4·2 g., 89%) was recrystallized from benzene–light petroleum (b. p. 30—50°) giving colourless needles, m. p. 121—122°, $[\alpha]_D^{20}$ −104·0° ± 2° (*c*, 1·0 in C_6H_6) (Found: C, 58·6; H, 4·6. $C_{13}H_{12}O_3NCl$ requires C, 58·8%; H, 4·6%).

The chloride (4·1 g.) was dissolved in ether (45 c.c.) and added to ethereal diazomethane (200 c.c., obtained from 12 g. of nitrosomethylurea). Next morning the solution was filtered and evaporated to dryness under reduced pressure. The residual oily (−)-1-diazo-4-methyl-3-phthalimidopentan-2-one was dissolved in ethyl acetate and precipitated with light petroleum; the oily diazo-ketone was dried *in vacuo* (yield, 3·7 g., 89%) and used without further purification.

Methyl (−)-β-phthalimido-γ-methylvalerate. A freshly prepared alkali-free suspension of silver oxide (obtained from 1·5 g. of silver nitrate) was added in four portions during 3 hr. to a refluxing solution of (−)-1-diazo-4-methyl-3-phthalimidopentan-2-one (3·7 g.) in methanol (15 c.c.), and the suspension heated under reflux for a further 4 hr. The hot suspension was treated with charcoal, filtered, and evaporated to dryness. The residue was extracted several times with light petroleum, the solvent from the combined extracts removed under reduced pressure, and the residual oil dissolved in carbon tetrachloride (15 c.c.) and filtered through a column of alumina (8 g.; activity IV). The pale yellow oily *methyl (−)-β-phthalimido-γ-methylvalerate* (2·70 g., 72%) obtained after evaporation of the solvent had the b. p. 125—130°/0·01 mm., $[\alpha]_D^{20}$ −6·27° ± 0·5° (*c*, 2·24 in MeOH) (Found: C, 65·5; H, 6·2. $C_{15}H_{17}O_4N$ requires C, 65·4; H, 6·2%).

(−)-β-Amino-γ-methylvaleric acid [(−)-β-leucine]. A solution of methyl (−)-β-phthalimido-γ-methylvalerate (1·85 g.) in acetic acid (9 c.c.) and 46% hydriodic acid (11 c.c.) was heated under reflux for 10 hr. After cooling, the phthalic acid was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in water, the solution extracted with ether (3 × 15 c.c.), and the aqueous layer again evaporated to dryness. The crystalline hydriodide of (−)-β-amino-γ-methylvaleric acid was dissolved in water (700 c.c.) and passed through a column of Amberlite IR-4B (20—50 mesh; 18 g.) at 200 c.c./hr. The column was washed with distilled water (700 c.c.), and the washings were evaporated *in vacuo*. (−)-β-Amino-γ-methylvaleric acid (820 mg., 93·2%) was twice recrystallized from absolute methanol–ether; it then melted at 202—210° (decomp.) and had $[\alpha]_D^{24}$ −39·2° ± 3° (*c*, 0·51 in H_2O), $[\alpha]_D^{20}$ −23·9° ± 1° (*c*, 0·88 in N-HCl), $[\alpha]_D^{20}$ + 4·6° ± 1° (*c*, 0·65 in N-NaOH) (Found: C, 54·7; H, 10·0. Calc. for $C_6H_{13}O_2N$: C, 54·9; H, 10·0%). Birkhofer and Storch (*loc. cit.*) reported m. p. 197—198° for the inactive form.

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The Preparation of 2 : 4-*Dinitrobenzoic Acid and* 2 : 4-*Dinitrophenylacetic Acid.*

By Jean P. Blanchard and Harlan L. Goering.

[Reprint Order No. 5339.]

In connection with another problem we have recently repeated a synthesis described by Brown and Campbell (*J.*, 1937, 1699) as an improved method for the preparation of 2 : 4-dinitrobenzoic acid. This method involves treating phenylacetic acid with fuming nitric acid and refluxing the resulting solution for 1 hr. Using this procedure we obtained a product in 66% yield (calculated as 2 : 4-dinitrobenzoic acid), which after recrystallization melted at 182·8—184° (Brown and Campbell, *loc. cit.*, report a 70% yield of material which after purification melted at 181—182°). This product, however, has a neutralisation equiv. of 228 corresponding to 2 : 4-dinitrophenylacetic acid (equiv., 226) rather than 2 : 4-dinitrobenzoic acid (equiv., 212). Moreover, the melting point of our material was depressed by authentic 2 : 4-dinitrobenzoic acid (m. p. 182·5—183·5°; equiv., 214) prepared by the chromic acid oxidation of 2 : 4-dinitrotoluene (Buehler and Calfee, *Ind. Eng. Chem. Anal.*, 1934, **6**, 351).

This evidence indicates that the product is 2 : 4-dinitrophenylacetic acid rather than the alleged 2 : 4-dinitrobenzoic acid. This was confirmed by chemical analysis (Found : C, 42·7; H, 2·6; N, 12·7. Calc. for $C_8H_6O_8N_2$: C, 42·5; H, 2·7; N, 12·4%) and by decarboxylation to 2 : 4-dinitrotoluene, m. p. and mixed m. p. 70—71° according to previously described procedures (Radziszewski, *Ber.*, 1870, **3**, 648; Gabriel and Meyer, *Ber.*, 1881, **14**, 823; Borsche, *Ber.*, 1909, **42**, 1310).

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2 : 3-*Diaminoanisole.*

By E. S. Lane and C. Williams.

[Reprint Order No. 5388.]

A convenient preparation of 2 : 3 diaminoanisole or phenetole was required in connection with the syntheses of new complexing agents for metals. Literature methods for the preparation of the corresponding dinitro-compounds, the reduction of which has provided the most direct route to these compounds, all require difficult isomer separations at some intermediate stage or use inconveniently large quantities of reagents (Easley and Sullivan, *J. Amer. Chem. Soc.*, 1952, **74**, 4450; Holleman, *Rec. Trav. chim.*, 1903, **22**, 271; Blanksma, *ibid.*, 1908, **27**, 49; Verkade and Witjens, *ibid.*, 1946, **65**, 361). A route to 2 : 3-diaminoanisole from *o*-anisidine was therefore investigated.

N-Nitration of *o*-anisidine in potassium ethoxide solution was carried out by a modification of Bamberger's preparation of aryl nitramines (*Ber.*, 1920, **53**, *B*, 2321), the more easily handled amyl nitrate being used in place of ethyl nitrate. The potassium salt of the nitramine was then caused to rearrange in sulphuric acid at −30°, and vacuum distillation then led to a simple separation of the main product, 3-nitro-*o*-anisidine, from the 5-isomer. 2 : 3-Diaminoanisole was obtained by catalytic reduction with hydrogen in approximately 29% overall yield. We have found this route (Brit. Patent Appln. 12710/1954) quicker, more convenient, and less expensive than those described in the literature.

Experimental.—**3-***Nitro*-o-*anisidine.* Potassium (45 g.) was dissolved in ethanol (150 ml.) in a nitrogen atmosphere, the solution cooled to 30°, and ether (184 ml.) added with stirring. Whilst the mixture was kept at −10°, amyl nitrate (151 ml.) was added and the mixture stirred for 15 min. *o*-Anisidine (128 ml.) was added in one portion, and the temperature then allowed to rise. The potassium salt of *o*-methoxyphenylnitramine was collected, washed with ether, air-dried (150 g.), and then added portionwise to concentrated sulphuric acid (240 ml.) and water (160 ml.) at −30°. The reaction mixture was left overnight, then poured into water (3 l.), and neutralised with ammonia solution (*d*, 0·88), and the precipitate collected, washed, dried,

and distilled. 3-Nitro-*o*-anisidine (61 g., 32%) distilled at 136—140°/0·5 mm. followed by 5-nitro-*o*-anisidine (19 g., 15%) (m. p. 139—140°). Above 230° a vigorous exothermic decomposition of the residual tar occurred. 3-Nitro-*o*-anisidine formed scarlet needles, m. p. 75° (methanol). Bantlin (*Ber.*, 1878, **11**, 2106) recorded m. p. 76°; Ingold and Ingold (*J.*, 1926, 1318) obtained m. p. 75—76° and m. p. 139—140° for the 3- and the 5-isomer, respectively. Acetylation of 3-nitro-*o*-anisidine with acetyl chloride–acetic anhydride gave the *diacetyl* derivative as very pale yellow needles, m. p. 129° (ethanol) (Found: C, 52·1; H, 4·6; N, 11·1. $C_{11}H_{12}O_5N_2$ requires: C, 52·4; H, 4·8; N, 11·1%). This is probably the compound described as the "acetate," m. p. 128°, by Blanksma (*Chem. Zentr.*, 1908, II, 1826); 3-nitroacet-*o*-anisidide, prepared by an unequivocal route by Ingold and Ingold (*loc. cit.*), had m. p. 158—159°.

2 : 3-*Diaminoanisole*. A mixture of 3-nitro-*o*-anisidine (250 g.), Raney nickel (50 g.), and ethanol (750 ml.) was shaken with hydrogen in a stainless-steel autoclave at 100 atm. pressure. The theoretical amount of hydrogen was absorbed during 1 hr. and the temperature rose to 120°. After cooling, the alcoholic solution was filtered, the Raney nickel twice washed with hot ethanol, and the combined solution concentrated. The residue was distilled, 2 : 3-*diaminoanisole* (b. p. 114—116°/0·5 mm.; yield 85—92%) showing a pronounced tendency to remain supercooled. Crystallisation was induced by seeding; the solid had m. p. 35—36° and darkened on exposure (Found: C, 60·3; H, 6·95; N, 20·6. $C_7H_{10}ON_2$ requires C, 60·8; H, 7·25; N, 20·3%). It was characterised as the dihydrochloride, m. p. 246° (water) (Found: C, 39·9; H, 5·6; N, 13·4; Cl, 33·9. Calc. for $C_7H_{12}ON_2Cl_2$: C, 39·8; H, 5·7; N, 13·3; Cl, 33·6%). Wrede and Strack (*Ber.*, 1929, **62**, 2051) record m. p. 250°. 2 : 3-*Dibenzamidoanisole*, white needles, melted at 185° (ethylene glycol) (Found: C, 72·7; H, 5·35; N, 8·0. $C_{21}H_{18}O_3N_2$ requires C, 72·8; H, 5·2; N, 8·1%).

The amino-groups were shown to be vicinal and an indication of the purity of the distillate was obtained by its conversion into 4-*methoxybenzo*-2 : 1 : 3-*selenadiazole* in over 95% yield by reaction of a solution of the amine in dilute hydrochloric acid with selenious acid. This formed yellow needles, m. p. 124—125° (ethanol) (Found: C, 39·3; H, 3·15; N, 13·3. $C_7H_6ON_2Se$ requires C, 39·4; H, 2·8; N, 13·1%).

We are indebted to Dr. I. G. M. Campbell (Southampton University) who suggested the possible value of the nitramine rearrangement for the preparation of *o*-nitro-amines, and to the Director, Chemical Research Laboratories, Teddington, for the provision of hydrogenation facilities.

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Organometallic Compounds containing Fluorocarbon Radicals.

LIVERSIDGE LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON MARCH 25TH, 1954.

By H. J. EMELÉUS.

THE rapid advance during the last twenty years in our knowledge of the chemistry of fluorocarbons has resulted in a situation which parallels that of classical organic chemistry towards the close of the last century. Fluorocarbon analogues of large numbers of aliphatic and alicyclic hydrocarbons have been prepared, together with many derivatives containing the familiar functional groups of organic chemistry. The comparative study of the two classes of compound has served to reveal similarities in physical properties and differences, which are often very great, in chemical behaviour. There was, however, until very recently, an outstanding gap in this rapidly developing subject. Practically nothing was known of the fluorocarbon analogues of organometallic and organometalloidal compounds. The field was attractive to us since it offered a possible route to the study of free fluorocarbon radicals. Moreover it was expected that, if compounds of this new type could be prepared, they would find applications in the synthesis of fluorocarbon derivatives. That an investigation of this sort should have been undertaken in a laboratory of inorganic chemistry can be justified by the fact that, as the subject has developed, the vacuum-techniques which are used for the quantitative manipulation of small amounts of volatile substances have proved singularly valuable. Indeed, many of the problems encountered could hardly have been approached in any other way. Before describing this work in detail I would like to express my indebtedness and thanks to all those who have collaborated in it, and to Dr. R. N. Haszeldine, who, in addition to participating in the experimental programme, has shared in its direction.

The obvious starting material for the preparation of organometallic compounds containing fluorocarbon radicals was trifluoroiodomethane, CF_3I, the analogue of methyl iodide. This was first prepared as a result of the study of the reactions of the halogen fluorides with the halogenomethanes, during which it was found that iodine pentafluoride reacted with carbon tetraiodide to form the desired compound. It also reacted with tetraiodoethylene to give pentafluoroiodoethane (Banks, Emeléus, Haszeldine, and Kerrigan, *J.*, 1948, 2188; Emeléus and Haszeldine, *J.*, 1949, 2948).

$$CI_4 \xrightarrow{IF_5} CF_3I \text{ (b. p. } -22{\cdot}5^\circ)$$

$$C_2I_4 \xrightarrow{IF_5} C_2F_5I \text{ (b. p. } 13^\circ) \xleftarrow{IF_5} C_2F_4I_2 \longleftarrow C_2F_4$$

Neither of these preparative methods was particularly convenient, however, and subsequent investigations have been greatly facilitated by the discovery of a general method for the preparation of fluoroalkyl iodides, depending on the reaction which occurs when the silver salt of a fully fluorinated aliphatic acid is heated with iodine (Haszeldine, *J.*, 1951, 584; 1952, 4259). The reaction shown below, for example, occurs at 150° and gives trifluoroiodomethane in high yield :

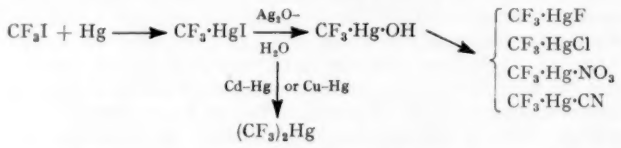
$$CF_3{\cdot}CO_2Ag + I_2 = CF_3I + CO_2 + AgI$$

Both trifluoroiodomethane and pentafluoroiodoethane are stable compounds which boil at $-22{\cdot}5^\circ$ and 13°, respectively, and are therefore very readily manipulated by the standard vacuum-technique, which was developed originally by Stock for the study of the hydrides of boron and silicon. The two compounds differ considerably from their alkyl analogues. Thus, it is impossible to replace the iodine atom by groups such as NO_2, NH_2 or CN by reactions which are applicable to the alkyl iodides. Moreover trifluoroiodomethane is readily hydrolysed by ethanolic alkali to give fluoroform ($CF_3I + KOH = CHF_3 + KOI$), a clear indication that it behaves as a positive iodine compound. Reaction with organic solvents also occurs under comparatively mild conditions favouring free-radical formation, and gives fluoroform. The behaviour of pentafluoroiodoethane is similar.

In one important respect there is a close analogy between methyl iodide and trifluoroiodomethane. Both show strong absorption of light in the region 2500—2700 Å and, on irradiation, undergo photochemical decomposition. The quantum yield is low in each case. That the

trifluoromethyl radical is produced in the photolysis is inherently probable, and this view is supported by the nature of the products obtained when the irradiation is done in presence of oxygen, chlorine, or cyanogen. Moreover, both ethylene and tetrafluoroethylene are polymerised when irradiated with trifluoroiodomethane (Banus, Emeléus, and Haszeldine, *J.*, 1950, **3041**; 1951, **60**; Haszeldine, *J.*, 1949, **2856**; 1953, **3761**). Similar polymerisations may be induced by heating the unsaturated compound to 200—300° with trifluoroiodomethane, and it is likely, therefore, that homolytic fission of the C–I bond also occurs under the action of heat.

These experiments provided a basis for attempting to prepare organometallic compounds containing trifluoromethyl radicals by a direct route and it was found that when trifluoroiodomethane was heated or irradiated with mercury a white crystalline compound, which proved to be trifluoromethylmercuric iodide, was formed. This, like the methyl analogue, reacted with an aqueous suspension of silver oxide to yield the base, $CF_3{\cdot}Hg{\cdot}OH$. The latter was readily



converted into the usual salts, but the preparation of bistrifluoromethylmercury proved to be impossible by the reactions which are applicable to the methyl analogue. It was necessary to use copper-, silver-, or cadmium-amalgam (Emeléus and Haszeldine, *J.*, 1949, **2948**, **2953**).

Bistrifluoromethylmercury was very different from dimethylmercury. It was a white crystalline solid which could be sublimed and dissolved, without decomposition, in both water and organic solvents. These properties suggest an analogy with mercuric chloride rather than with the typically covalent dimethyl compound. The aqueous solution had a small but definite electrical conductivity. That this was not due to formation of the base, $CF_3{\cdot}Hg{\cdot}OH$, is shown by the fact that no fluoroform was evolved from the aqueous solution. No experimental work has so far been done to determine the nature of the ions in aqueous solution, but it is unlikely that CF_3^- is present and more probable that a complex anion such as $[Hg(CF_3)_4]^{2-}$ is formed.

The direct reaction of trifluoroiodomethane with other metals has not yet been studied in detail. There were indications that the most electropositive elements (*e.g.*, sodium) abstracted fluorine from the trifluoromethyl radical when heated to a temperature sufficiently high to initiate reaction. Some evidence of the formation of volatile products, which may be organometallic derivatives, has been obtained in preliminary experiments on the reaction of trifluoroiodomethane with elements such as indium and germanium, and in addition work has been done on Grignard and Grignard-type compounds obtained from magnesium, lithium, and zinc, as is described below.

The reaction of trifluoroiodomethane with non-metals has been examined in much greater detail and has yielded a number of new products of outstanding interest. The experimental approach in this case was essentially the same as that used with mercury. Trifluoroiodomethane was heated with an excess of the element (phosphorus, arsenic, antimony, sulphur, or selenium), in either a sealed tube or a stainless-steel autoclave. The temperature at which reaction occurred was roughly the same as that at which the polymerisation of ethylene and tetrafluoroethylene was induced (200—250°). One may therefore assume that homolytic fission of the C–I bond occurred and that some of the iodine set free reacted with excess of the element used. The products obtained in this way are shown in Table 1.

These products were separated either by fractionation in the vacuum-apparatus or by normal distillation techniques. It is convenient first to consider the phosphorus and arsenic derivatives together, since they show many points of similarity. The yields of the types $(CF_3)_3M$, $(CF_3)_2MI$, and $CF_3{\cdot}MI_2$ are in each case approximately in the ratio 7 : 2 : 1, and there is evidence that an equilibrium is set up between these substances and the tri-iodide, MI_3, which is also formed in the reaction. All six of the compounds are decomposed when heated with an excess of aqueous alkali, and the fluorine is liberated quantitatively as fluoroform. Direct measurement of the gaseous fluoroform produced has greatly facilitated analysis. Both trimethylphosphine and trimethylarsine are stable under these conditions. The electronegative trifluoromethyl groups exert a strong influence on the phosphorus and arsenic atoms in the tristrifluoromethyl derivatives and attempts to prepare co-ordination compounds analogous to those formed by trimethyl-phosphine and -arsine have so far been unsuccessful. The effect of negative groups is

also seen in other cases. Thus, triarylphosphines do not form compounds with carbon disulphide, though they do so with sulphur.

Both tristrifluoromethylphosphine and tristrifluoromethylarsine are readily oxidised by air. They also combine with chlorine and give the quinquevalent derivatives $(CF_3)_3PCl_2$ and

TABLE 1. *Products of the reaction of trifluoroiodomethane with non-metals.*

Element (& ref.)	Product	B. p.	Element (& ref.)	Product	B. p.
P (1)	$(CF_3)_3P$	17·5°	Sb (3)	$(CF_3)_2Sb$	72°
	$(CF_3)_2PI$	73		$(CF_3)_2SbI$	—
	$CF_3{\cdot}PI_2$	69°/29 mm.	S (4)	$(CF_3)_2S_2$	35
As (2)	$(CF_3)_3As$	33·3		$(CF_3)_2S_3$	86·5
	$(CF_3)_2AsI$	92		$(CF_3)_2S_4$	135
	$CF_3{\cdot}AsI_2$	154	Se	$(CF_3)_2Se$	−1
				$(CF_3)_2Se_2$	70

(1) Bennett, Emeléus, and Haszeldine, *J.*, 1953, 1565; 1954, in the press. (2) Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2552; Emeléus, Haszeldine, and Walaschewski, *J.*, 1953, 1552; Walaschewski, *Chem. Ber.*, 1953, **86**, 272. (3) Dale, Emeléus, and Haszeldine, Abstr. Amer. Chem. Soc. Meeting, Atlantic City, Sept. 1952, p. 14K; Robison, unpublished results. (4) Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2198, 2549; Haszeldine and Kidd, *J.*, 1953, 3219.

$(CF_3)_3AsCl_2$, which are unstable above their boiling points. The compound $(CF_3)_3AsCl_2$ is converted by silver fluoride into $(CF_3)AsF_2$. By using an excess of chlorine it has proved possible to convert chlorobistrifluoromethylphosphine into bistrifluoromethylphosphorus trichloride, but this also loses chlorotrifluoromethane. The compound $(CF_3)_2AsCl_3$ may be prepared similarly.

$$(CF_3)_3P + Cl_2 \longrightarrow (CF_3)_3PCl_2 \longrightarrow (CF_3)_2PCl + CF_3{\cdot}Cl \xrightarrow{Cl_2} (CF_3)_2PCl_3$$

No definite addition compounds with bromine or iodine have been obtained, though there is some evidence that addition of bromine occurs at low temperatures. At higher temperatures products such as $(CF_3)_2AsBr$ and $CF_3{\cdot}AsBr_2$ are formed, together with bromotrifluoromethane. Tristrifluoromethyl-phosphine and -arsine react with iodine only when heated, and give the mono- and di-iodo-compounds.

The iodine atoms in the mono- and di-iodides are readily replaced by other groups; for example, by reaction with the appropriate silver salt. Table 2 shows a number of typical derivatives which have been obtained by this and other reactions.

TABLE 2. *Derivatives of fluoroalkyl-phosphines and -arsines.*[a]

Product	Method	B. p.	Product	Method	B. p.
$(CF_3)_2PCN$	$(CF_3)_2PI + AgCN$	48°	$(CF_3)_2AsCN$ ...	$(CF_3)_2AsI + AgCN$	89·5
$(CF_3)_2PCl$	$(CF_3)_2PI + AgCl$	21	$(CF_3)_2AsCl$	$(CF_3)_2AsI + AgCl$	46
$CF_3{\cdot}PCl_2$	$CF_3{\cdot}PI_2 + AgCl$	37	$CF_3{\cdot}AsCl_2$	$CF_3{\cdot}AsI_2 + AgCl$	71
			$(CF_3)_2AsBr$	$(CF_3)_3As + Br_2$	59·5
$(CF_3)_2PH$	$(CF_3)_2PI + H_2$	1	$(CF_3)_2AsF$	$(CF_3)_2AsI + AgF$	25
$CF_3{\cdot}PH_2$	$CF_3{\cdot}PI_2 + LiAlH_4$	−26·5	$(CF_3)_2AsH$	$(CF_3)_2AsI + LiAlH_4$	19
$(CF_3)_4P_2$	$(CF_3)_2PI + Hg$	83—84	$CF_3{\cdot}AsH_2$	$CF_3{\cdot}AsI_2 + LiAlH_4$	−20
			$(CF_3)_4As_2$	$(CF_3)_2AsI + Hg$	106—107
			$(CF_3)_4As_2O$	$(CF_3)_2AsI + HgO$	97—100

[a] See references in Table 1.

The derivatives in which one or two atoms of iodine are replaced by other atoms or groups by interaction with a silver salt call for little comment. The substituted phosphines and arsines are of greater interest. Bistrifluoromethylphosphine is best prepared by reducing iodobistrifluoromethylphosphine with hydrogen in the presence of Raney nickel. The most convenient method for the preparation of trifluoromethylphosphine, $CF_3{\cdot}PH_2$, is the hydrolysis of di-iodotrifluoromethylphosphine in concentrated aqueous solution, followed by freeze-drying of the solution. During the latter process the phosphonous acid undergoes partial decomposition:

$$CF_3{\cdot}PI_2 \xrightarrow{H_2O} CF_3{\cdot}P(OH)_2 \longrightarrow CF_3{\cdot}PH_2$$

Both of the substituted phosphines are spontaneously inflammable. Unlike dimethylphosphine, bistrifluoromethylphosphine forms no addition compounds with methyl iodide, carbon disulphide, silver iodide, or chloroplatinic acid. The two substituted arsines are readily prepared by reducing the iodo-compounds with lithium aluminium hydride in di-*n*-butyl ether. They, too, do not form addition compounds as do the methylarsines.

The reactions leading to formation of the diphosphine and diarsine occur readily at room

temperature and are of special interest. No methyl analogue of tetrakistrifluoromethyldiphosphine is known : the arsenic compound, $(CF_3)_4As_2$, corresponds to cacodyl. Both of the fluorinated substances are comparatively stable, though they are oxidised in air. They differ from other trifluoromethyl derivatives of phosphorus in that, on hydrolysis by aqueous alkali, both fluoride ion and fluoroform are produced. It seems probable that the initial step in the hydrolysis will involve cleavage of the bond between the two metalloidal atoms, as shown below for the diarsine, and that the nature of the hydrolysis products can be explained in terms of the behaviour of the intermediates postulated :

$$(CF_3)_2As{\cdot}As(CF_3)_2 \xrightarrow{H_2O} (CF_3)_2AsH + (CF_3)_2As{\cdot}OH$$

Evidence on the hydrolysis of the hypothetical acid, $(CF_3)_2As{\cdot}OH$, is furnished by the reaction of iodobistrifluoromethylarsine with aqueous sodium hydroxide, all of the fluorine being evolved as fluoroform (2 mols.). Bistrifluoromethylarsine, on hydrolysis under conditions identical with those used in the experiments with tetrakistrifluoromethyldiarsine, gives 66% of the trifluoromethyl groups as fluoroform and 34% as fluoride and carbonate. By the mechanism postulated, 1 mole of the diarsine should give 2 moles of fluoroform by alkaline hydrolysis of the acid $(CF_3)_2As{\cdot}OH$ and ($\frac{2}{3} \times 2$) moles from $(CF_3)_2AsH$, *i.e.*, a conversion of 83% of the fluorine into fluoroform, and the balance into fluoride. This agrees well with the experimentally determined value of 84% conversion into fluoroform. These experiments provide good evidence for the mechanism of hydrolysis of the diarsine, though they do not explain the breakdown of some of the trifluoromethyl groups to fluoride. Trifluoromethylarsine, $CF_3{\cdot}AsH_2$, also hydrolyses under similar conditions to fluoride, fluoroform, carbonate, and arsenite, but the proportion of fluoroform is only 12—14% and an amorphous yellow solid, which may be a polymerised unsaturated arsenic hydride, is also produced.

The behaviour of tetrakistrifluoromethyldiphosphine on hydrolysis with aqueous alkali is similar to that of the diarsine in that three of the four trifluoromethyl groups appear as fluoroform. The residual fluorine is, however, present partly as fluoride (9%) and partly (13%) as the salt of a relatively stable trifluoromethyl acid of phosphorus, which has not been identified with certainty. If the hydrolytic fission of the P–P bond is postulated as the initial step, one may again attempt to correlate the observed distribution of fluorine among the hydrolytic products with that predicted from the products of the initial reaction :

$$(CF_3)_2P{\cdot}P(CF_3)_2 \xrightarrow{H_2O} (CF_3)_2PH + (CF_3)_2P{\cdot}OH$$

The alkaline hydrolysis of iodobistrifluoromethylphosphine yields all of the fluorine as fluoroform. Hydrolysis under identical conditions of the substituted phosphine $(CF_3)_2PH$, prepared by the method already described, shows that half of the fluorine is liberated as fluoroform, 18% as fluoride and 28% as the salt of a trifluoromethyl acid of phosphorus, the infra-red spectrum of which is identical with that of the salt obtained in the hydrolysis of the diphosphine. The mechanism postulated would thus predict the formation of 75% of fluoroform (*i.e.*, 3 mols.), 9% of fluoride and 14% of the trifluoromethyl acid, in good agreement with the experimental figures.

Interesting support for this mechanism is given by experiments on the reaction of tetrakisdimethyldiphosphine with water or dilute acid at 100°. Half of the fluorine appears as fluoroform and, in addition, both trifluoromethylphosphine, $CF_3{\cdot}PH_2$, and bistrifluoromethylphosphine, $(CF_3)_2PH$, may be isolated. The former was identified by its infra-red spectrum, and it is known to be one of the products of reaction of bistrifluoromethylphosphine with water at

$$(CF_3)_2P{\cdot}P(CF_3)_2 \xrightarrow{H_2O} (CF_3)_2PH + (CF_3)_2P{\cdot}OH \xrightarrow{H_2O} CF_3{\cdot}PHO{\cdot}OH + CHF_3 \xrightarrow[100°]{H_2O} CHF_3$$

$$(CF_3)_2PH \xrightarrow{H_2O\ (100°)} CF_3{\cdot}PH_2 + F^- + CO_3^{2-}$$

120°. The phosphinic acid $CF_3{\cdot}PHO{\cdot}OH$, shown in the reaction scheme, has been synthesised (see below) and is found to be decomposed by water at 100°. Thus the general picture of the hydrolysis mechanism is established, though, for both the diphosphine and the diarsine, it is desirable to extend the work by studying products of hydrolysis under more diverse conditions.

Experiments on the hydrolysis and oxidative hydrolysis of iodotrifluoromethyl-phosphines and -arsines has yielded several new acids with interesting properties associated with the

presence of the strongly negative trifluoromethyl group. The formulæ of the acids of phosphorus are shown in Table 3, together with values of the dissociation constants and those of their methyl analogues. Trifluoromethylphosphinic acid, $CF_3 \cdot PHO \cdot OH$, is formed in the slow hydrolysis

TABLE 3. *Trifluoromethyl and methyl acids of phosphorus.*

$CF_3 \cdot PHO \cdot OH$	$K = 10 \times 10^{-3}$	$CH_3 \cdot PHO \cdot OH$	$K = -$
$CF_3 \cdot PO(OH)_2$	$K_1 = 6{\cdot}8 \times 10^{-2}$	$CH_3 \cdot PO(OH)_2$	$K_1 = 3{\cdot}3 \times 10^{-3}$
	$K_2 = 1{\cdot}2 \times 10^{-4}$		$K_2 = 1{\cdot}2 \times 10^{-8}$
$(CF_3)_2PO \cdot OH$	$K = \infty$	$(CH_3)_2PO \cdot OH$	$K = 8{\cdot}3 \times 10^{-4}$

by cold water of either di-iodotrifluoromethylphosphine or iodobistrifluoromethylphosphine. The bistrifluoromethylphosphinic acid, formed initially from iodobistrifluoromethylphosphine, is unstable and, by loss of one CF_3 group as fluoroform, yields $CF_3 \cdot PHO \cdot OH$ which is a moderately strong monobasic acid with weak reducing properties. It is, for example, oxidised by per-

$$(CF_3)_2PI + 2H_2O = CF_3 \cdot PHO \cdot OH + CHF_3 + HI$$
$$CF_3 \cdot PI_2 + 2H_2O = CF_3 \cdot PHO \cdot OH + 2HI$$

manganate, though not by iodine solution. It has not been isolated in the pure state, since it is volatile in water vapour at reduced pressure. Above pH 11, or when the aqueous solution is heated to 100°, fluoroform is lost quantitatively. The infra-red spectrum of the monosodium salt shows bands which may be attributed to P–H and P=O vibrations, in keeping with the formula shown in Table 3, in which the phosphorus atom is four-co-ordinated.

The acids $CF_3 \cdot PO(OH)_2$ and $(CF_3)_2PO \cdot OH$ have both been isolated in the pure state and shown to be di- and mono-basic, respectively. The first is a white crystalline solid and is prepared by hydrolysing compounds of the type $CF_3 \cdot PX_2$ or $(CF_3)_2PX$ (X = Cl or I), or by controlled hydrolysis of $(CF_3)_3P$, followed by oxidation. The second acid is a liquid (b. p. 182°) and is most conveniently prepared by the following method (Paul, unpublished observations) :

$$(CF_3)_2PI \xrightarrow{AgCl} (CF_3)_2PCl \xrightarrow{Cl_2} (CF_3)_2PCl_3 \xrightarrow{H_2O} (CF_3)_2PO \cdot OH$$

It is completely dissociated in aqueous solution, in marked contrast to the methyl analogue.

The two iodoarsines, $(CF_3)_2AsI$ and $CF_3 \cdot AsI_2$, differ from their phosphorus analogues in that both are stable to water, although readily decomposed by alkali. Attempts to prepare the free acids $(CF_3)_2As \cdot OH$ and $CF_3 \cdot As(OH)_2$ have so far been inconclusive. Oxidative hydrolysis of the mono- and di-iodo-compounds has, however, yielded two substituted arsonic acids, the dissociation constants of which are compared in Table 4 with those of their methyl analogues.

TABLE 4. *Trifluoromethyl and methyl acids of arsenic.*

$(CF_3)_2AsO \cdot OH$	$K = 4 \times 10^{-2}$	$(CH_3)_2AsO \cdot OH$	$K = 7{\cdot}5 \times 10^{-7}$
$CF_3 \cdot AsO(OH)_2$	$K_1 = 7{\cdot}7 \times 10^{-2}$	$CH_3 \cdot AsO(OH)_2$	$K_1 = 2{\cdot}5 \times 10^{-4}$
	$K_2 = 5 \times 10^{-6}$		$K_2 = 5{\cdot}7 \times 10^{-9}$

The trifluoromethylarsonic acids are highly ionised in aqueous solution and much stronger than the corresponding methyl acids. Since water is unsuitable as a solvent for differentiating between strong acids, conductivity measurements have been made in anhydrous acetic acid, in which the acid strengths are found to be in the order: $H_2SO_4 > HCl$, $CF_3 \cdot PO(OH)_2 > (CF_3)_2AsO \cdot OH > CF_3 \cdot AsO(OH)_2 \gg CF_3 \cdot CO_2H$, HNO_3, $C_3F_7 \cdot CO_2H$.

Trifluoromethylarsonic acid undergoes dehydration *in vacuo*, first to a pyro-acid and then to an anhydride, both of which revert to the ortho-form in water :

$$CF_3 \cdot AsO(OH)_2 \xrightarrow{33°/10^{-3}\ mm.} CF_3 \cdot As(O)(OH)-O-As(O)(OH) \cdot CF_3 \xrightarrow{73°/10^{-3}\ mm.} CF_3 \cdot AsO_2$$
$$CF_3 \cdot AsO_2 \xrightarrow{H_2O} CF_3 \cdot AsO(OH)_2$$

Methylarsonic acid also forms a pyro-acid on dehydration, though its anhydride has not been reported. No conclusive evidence of pyro-acid or anhydride formation was obtained for the second of the two new acids of arsenic.

Mixed arsines may be prepared by two methods. In the first the Grignard reaction is applied to iodotrifluoromethyl arsines. Thus, $CF_3 \cdot AsI_2$ and methylmagnesium iodide gave $CF_3 \cdot AsMe_2$, and a similar reaction could certainly be used with the fluoroalkyl iodides of other elements. In the second, it has been found that, when tristrifluoromethylarsine is heated to

about 230° with methyl iodide, an exchange reaction occurs, and mixed alkyl-fluoroalkylarsines may be isolated from the product. The reaction mechanism probably involves the formation of an unstable quaternary compound, thus :

$$(CF_3)_3As + MeI \longrightarrow \left[(CF_3)_3As\begin{matrix}\nearrow Me\\ \searrow I\end{matrix}\right] \longrightarrow (CF_3)_2AsMe + CF_3I$$

Similar exchange reactions have been observed with tristrifluoromethylphosphine and there are indications that the reactions may be even more general.

The trifluoromethylantimony compounds are less stable than the arsenicals. Thus, tristrifluoromethylstibine decomposes thermally at about 200°, whereas the arsenic analogue is stable up to about 350° (Ayscough, unpublished observations). Iodobistrifluoromethylstibine also disproportionates readily and has not yet been fully characterised. It resembles the monoiodoarsenic compound in that it reacts readily with mercury and forms the distibine, $(CF_3)_4Sb_2$. Tristrifluoromethylstibine also adds on chlorine to form $(CF_3)_3SbCl_2$ which, with water, gives a dihydrate, $(CF_3)_3SbCl_2,2H_2O$. The latter is decomposed by warm water to a strong monobasic acid, which has been characterised as the silver salt $Ag[Sb(CF_3)_3(OH)_3]$. The free acid has not yet been isolated, but the pyridine salt is crystalline and may be recrystallised from organic solvents (Moss, unpublished results). When it is treated with hydrochloric or hydrobromic acid the following transformations occur :

$$PyrH[Sb(CF_3)_3Br_3] \xleftarrow{HBr} PyrH[Sb(CF_3)_3(OH)_3] \xrightarrow{HCl} PyrH[Sb(CF_3)_3Cl_3]$$

Pyr = Pyridine

This behaviour is in accord with the general chemistry of other antimonic acids and, when the field has been more fully explored, it is likely that the fluoroalkyl-acids will be found to be much stronger and better defined than other antimonic acids.

The reaction of trifluoroiodomethane with sulphur and selenium gives, from sulphur, the polysulphides $(CF_3)_2S_2$, $(CF_3)_2S_3$, and $(CF_3)_2S_4$ and, from selenium, $(CF_3)_2Se$ and $(CF_3)_2Se_2$. In the reaction with sulphur the main product is the disulphide $(CF_3)_2S_2$. Both the di- and the tri-sulphide are formed in an interesting reaction between carbon disulphide and iodine pentafluoride in a steel autoclave at 100° (Haszeldine and Kidd, *J.*, 1953, 3219).

The structure of the disulphide follows from the reactions :

$$Hg(S{\cdot}CF_3)_2 \xleftarrow[\text{light}]{Hg} C_2S_2F_6 \xrightarrow[300°]{Cl_2} 2CF_3Cl + S_2Cl_2$$

Chlorine gives a yield of chlorotrifluoromethane in excess of 90%, and thus shows the presence of two CF_3 groups. The reaction with mercury occurs in ultra-violet light and shows the presence of the $S{\cdot}CF_3$ group in the disulphide. The mercurial is a white crystalline solid which may be sublimed, and is a salt of the thiol, $CF_3{\cdot}SH$, which may be prepared in the pure state by decomposing bistrifluoromethylthiomercury with dry hydrogen chloride, $Hg(S{\cdot}CF_3)_2 + 2HCl = HgCl_2 + 2CF_3{\cdot}SH$. The thiol is a gas (b. p. −37°) which is decomposed by water with the formation of carbonyl sulphide, $CF_3{\cdot}SH \xrightarrow{-HF} CSF_2 \xrightarrow{H_2O} COS + 2HF$.

The monosulphide, $(CF_3)_2S$, is not a product of the reaction of trifluoroiodomethane with sulphur, but is produced together with sulphur when the disulphide is irradiated with ultra-violet light. The thiol is much more stable than the disulphide and resists hydrolysis by aqueous alkali, whereas the di-, tri-, and tetra-sulphides are completely decomposed, all of the fluorine being converted into fluoride. This stability parallels that of bistrifluoromethyl ether, $(CF_3)_2O$, and of the amine, $(CF_3)_3N$.

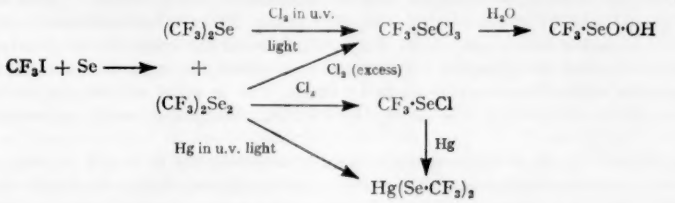
Bistrifluoromethyl disulphide, when mixed with chlorine and irradiated in ultra-violet light, gives trifluoromethylsulphenyl chloride, $CF_3{\cdot}SCl$ (b. p. 0°). The latter, on treatment with trifluoromethanethiol gives bistrifluoromethyl disulphide, while, with hydrogen sulphide, the

$$(CF_3)_2S_2 \xrightarrow[(h\nu)]{Cl_2} CF_3{\cdot}SCl \begin{cases}\xrightarrow{CF_3{\cdot}SH} CF_3{\cdot}S{\cdot}S{\cdot}CF_3\\ \xrightarrow{H_2S} CF_3{\cdot}S{\cdot}S{\cdot}S{\cdot}CF_3\end{cases}$$

trisulphide is produced. These reactions serve to establish the interrelationship of the compounds. Electron-diffraction studies have shown that the di- and the tri-sulphide contain a

bent chain of sulphur atoms. Trifluoromethanesulphonic acid is obtained by oxidising the sulphur compounds with hydrogen peroxide. It may be isolated as the barium or the sodium salt, from which the free acid is liberated by concentrated sulphuric acid. Trifluoromethanesulphonic acid resembles sulphuric acid in many respects: it is a fuming oily liquid and is one of the strongest known sulphur acids. Reaction with phosphorus pentachloride gives trifluoromethanesulphonyl chloride, b. p. 32° (Kidd, unpublished results).

Reaction of trifluoroiodomethane with selenium yields the monoselenide and diselenide in a ratio of about 2 : 1. The former is much more readily hydrolysed than the monosulphide. The reactions of the latter which have so far been studied are shown below (Dale, Emeléus, and Haszeldine, Abstr. Amer. Chem. Soc. Meeting, Atlantic City, Sept. 1952, p. 14K):



There is a general resemblance to the sulphur compounds and such differences as exist appear to follow the general trends of Group VI. Thus, the compound $CF_3{\cdot}SeCl_3$ is much more stable than $CF_3{\cdot}SCl_3$. Some evidence of the formation of the latter compound has been obtained, though its dissociation pressure at room temperature is high. The mercurial resembles its sulphur analogue in general characteristics, though the corresponding selenol, $CF_3{\cdot}SeH$, has not yet been prepared. A few experiments on the reaction between trifluoroiodomethane and tellurium have failed to yield either a mono- or a di-telluride. It is possible, however, that these compounds can be prepared by this route under modified conditions, though their thermal stability may be low.

An alternative method for the preparation of fluoroalkyl organometallic and organometalloidal compounds is by use of Grignard-type reagents. They are less readily prepared, and less stable, than Grignard reagents containing an alkyl or aryl group. Nevertheless, by using pure magnesium, and with suitable initiation of the reaction, trifluoromethylmagnesium iodide has been obtained in solution in ethyl or butyl ether. The solutions are relatively stable at $-30°$ to $-10°$ and have been shown to exhibit normal reactions, such as the formation of fluoroform with water, of fluorinated acids with carbon dioxide, and of ketones with acyl chlorides (Haszeldine, *Nature*, 1951, **167**, 139; **168**, 1028; *J.*, 1954, 1273). Pentafluoroiodoethane and heptafluoroiodopropane also yield magnesium derivatives, and the latter has given an 80% yield in solution at low temperatures (Haszeldine, *J.*, 1952, 3423; 1953, 1748). Heptafluoro-*n*-propylzinc iodide has also been prepared by the reaction of heptafluoroiodopropane with zinc in a solvent such as dioxan or dibutyl ether, and from dioxan solution the solvated compound $C_3F_7{\cdot}ZnI,C_4H_8O_2$ was isolated. This, when heated in vacuum, lost dioxan and gave heptafluoro-*n*-propylzinc iodide (Haszeldine and Walaschewski, *J.*, 1953, 3607).

An alternative route for the preparation of perfluoroalkyl Grignard compounds is by radical exchange (Haszeldine, unpublished observations). Thus phenylmagnesium iodide reacts with heptafluoroiodopropane and an equilibrium is set up ($PhMgI + C_3F_7I \rightleftharpoons C_3F_7{\cdot}MgI + PhI$). Another exchange reaction which is potentially of great importance is that between lithium alkyls and perfluoroalkyl iodides. Here the exchange is almost complete:

$$MeLi + C_3F_7I = C_3F_7Li + MeI$$

The extremely reactive perfluoroalkyl-lithium must, like the Grignard compound, be manipulated at below $-10°$. Heptafluoropropyl-lithium can thus be prepared in solution in over 80% yield and trifluoromethyl-lithium in about 20% yield. The lithium compounds undergo a variety of reactions of the normal types with organic functional groups. Of particular interest, however, is their reaction with silicon tetrachloride. Solutions of trifluoromethylmagnesium iodide react with silicon tetrachloride and give $(CF_3)_2SiCl_2$ in low yield. Preliminary experiments have shown that the perfluoroalkylsilicon compounds are obtained in much better yields from solutions of the perfluoroalkyl-lithiums. These experiments offer a clear route for the preparation of perfluoroalkylsilicones, and it may well prove possible to use these reagents to

obtain other perfluoroalkyl derivatives, which are not accessible by the direct method depending on the reaction of the element with a fluoroalkyl iodide.

A different approach to the same problem is by the electrochemical fluorination of organometallic compounds with the object of fluorinating alkyl groups directly. The process of electrochemical fluorination has been widely applied to the preparation of fully fluorinated organic compounds (Brice, Dresdner, Francis, Harland, Hogg, Pearlson, Simons, and Wilson, *Trans. Electrochem. Soc.*, 1949, **95**, 47). It depends on the electrolysis of a solution of the substance to be fluorinated in anhydrous hydrogen fluoride, with a nickel anode, and at a voltage lower than that at which free fluorine is evolved. When applied to the electrochemical fluorination of dimethyl sulphide the compounds $CF_3{\cdot}SF_5$ and $(CF_3)_2SF_4$ were obtained, the latter in small yield (Clifford, El-Shamy, Emeléus, and Haszeldine, *J.*, 1953, 2372). These experiments demonstrate the possibility of converting a methyl group directly into trifluoromethyl, though not without considerable loss arising from the breakdown of the molecule to give both sulphur hexafluoride and carbon tetrafluoride. In other cases solvolysis of organometallic compounds with the liberation of hydrocarbon is likely to occur, but in spite of this the method clearly warrants closer study as it offers the advantages of simplicity and ready accessibility of raw materials.

When the progress made so far in this new field is reviewed one is struck by the great differences which exist between organometallic compounds containing fluoroalkyl and alkyl groups. Structurally the two types are similar and there is also a general similarity in physical properties, but the chemical properties have little in common. This can be explained qualitatively in terms of the high negativity of the fluoroalkyl groups, but much remains to be done before any quantitative discussion of the problem can be attempted. The results obtained thus support the view that, in general, fluorocarbon chemistry is quite distinct from hydrocarbon chemistry, and that progress may well be hindered by too great a dependence on analogy in considering future developments.

The work described serves to open up the chemistry of fluoroalkyl organometalloidal compounds, though even in the field so far explored many gaps remain. Much progress has been made with a simple preparative method based on the direct reaction of fluoroalkyl iodides with non-metals. Even allowing for the possibility that derivatives of some other elements may be produced in the same way under more closely controlled conditions, it is unlikely that many more will yield to this approach. Of the two other synthetic methods described, the Grignard reagent holds a promise of fairly general applicability. Electrochemical fluorination on the other hand may well prove to be very limited in its scope. There remains, therefore, a need for yet other methods of synthesis with which to prepare fluoroalkyl derivatives of the more electropositive elements, and of elements such as lead and tin, the alkyl derivatives of which are well known. It is in the search for these compounds, which are unknown at present, that some of the new non-metallic fluoroalkyl derivatives may be useful.

Physicochemical problems associated with the new organometallic compounds are many and, for the most part, are untouched. Indeed, with a few exceptions, this is true of the whole field, and one may hope that the greater availability of fluorocarbons and their derivatives will lead to a more intensive study of kinetic problems in particular. Major experimental difficulties are likely to be encountered in studying free fluorocarbon radicals as their reactivity is so much greater than that of hydrocarbon radicals. This, indeed, has been our own experience in studying the kinetics of the pyrolysis of tristrifluoromethylarsine. Such difficulties are, however, a challenge which I hope some of my audience will accept.

The iso*Quinoline Alkaloids.*

CENTENARY LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT THE UNIVERSITY, EDINBURGH, ON TUESDAY, APRIL 27TH, 1954, AND AT BURLINGTON HOUSE ON THURSDAY, MAY 6TH, 1954.

By R. H. MANSKE.

I DO not propose to give a chronological account of the chemistry of *iso*Quinoline Alkaloids but I cannot refrain from noting two dates. The first is 1817 when Robiquet isolated narcotine from opium, and this is, for good reasons, the birth of alkaloid chemistry. The second landmark was 1885 when Hoogewerf and van Dorp isolated *iso*quinoline from coal-tar distillates. In terms of progress in the sciences as of to-day this interval of sixty-eight years between the above two events is indeed a long one, particularly since no real progress could be made in the elucidation of the structure of an *iso*quinoline alkaloid until the structure of the *iso*quinoline nucleus was clear We, who sometimes determine the structure of an alkaloid in a single day, should pause before we bask in complacency. If we had to determine not only the positions of the methoxyl groups in hemipinic acid but also the relative positions of the carboxyl groups our progress would indeed be much slower, and if in addition to these formidable difficulties we were not very certain of atomic weights we should probably leave the structure of a new alkaloid to the mercies of posterity.

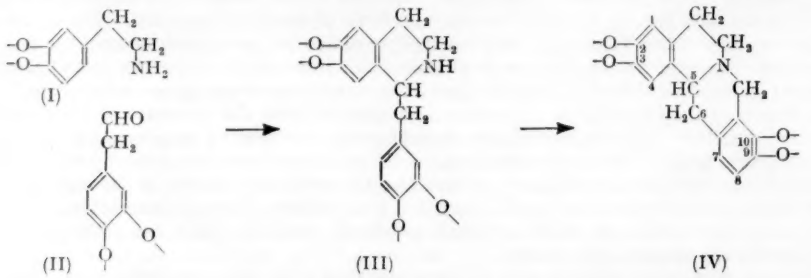
I have made these observations to show you that I am not unmindful of the skill of our predecessors and if I should appear to give short notice to a great work I do so only because I must make haste and may not tarry too long in any one paradise.

The *iso*quinoline nucleus can be conceived as the nucleus formed by the fusion of a benzene and a pyridine nucleus although there are no chemical reactions which can accomplish such a union with the necessary loss of two carbon atoms. In Nature the nucleus is invariably substituted and in all examples save papaverine the hetero-ring is in the tetrahydro-form. The oxygen-substituents and the four hydrogen atoms furnish a clue to the biogenetic origin of the compounds, and indeed there is a strong hint that the building blocks used by the plant and by the chemist are at least formally similar. Without the *O*-substituents the benzene nucleus lacks activated positions and ring closure becomes practicallly impossible *in vitro* and presumably also *in vivo*. Consequently the benzene portion of the *iso*quinoline of natural origin carries an *O*-substituent in the position *para* to that of ring closure and generally one and sometimes two more oxygen atoms. By extrapolating backward it is possible to recognize dihydroxyphenylalanine or its decarboxylated derivative as one of the main precursors of *iso*quinolines. This important compound has long been known as a product of plant anabolism, and ample evidence is now available that at least the animal cell can prepare tyrosine from phenylalanine by hydroxylation.[1] The added oxygen always enters *ortho* to the one already present and it is therefore not surprising that the lignins have the oxygens in the 3 : 4- (or vanillin) and in the 3 : 4 : 5-positions. There is here a suggestion that the alkaloids and the lignins have common ancestors and that tyrosine or a near relative is that ancestor. There is a sufficiency of examples of the co-presence of alkoxyarylethylamines and the corresponding alkoxy*iso*quinolines in the same plant to lend conviction to the hypothesis that the latter are derived from the former.

The exact mechanism by which this synthesis takes place is open to speculation. Certainly the plant cell does not cause an aroyl halide to react with the amine in the presence of strong alkali and then treat the resultant amide with phosphoric oxide in boiling toluene. Nor does it then treat the resultant base with methyl iodide and reduce the product with zinc dust in glacial acetic acid. The early suggestion by Robert Robinson and the later work of Schöpf [2] and of Hahn [3,4,5] and their associates have shown that the dihydroxyamino-compounds react with aldehydes, under conditions of pH and temperature probable in a plant, to give *iso*quinolines in excellent yields. That enzymes also play a rôle, though not necessarily an

[1] A. R. Moss and R. Schoenheimer, *J. Biol. Chem.*, 1940, **135**, 415.
[2] C. Schöpf and H. Bayerle, *Annalen*, 1934, **513**, 190.
[3] G. Hahn and H. Wassmuth, *Ber.*, 1934, **67**, 696.
[4] G. Hahn and O. Schales, *Ber.*, 1935, **68**, 24.
[5] G. Hahn and F. Rumpf, *Ber.*, 1938, **71**, 2141.

important one, is shown by the almost universal optical activity of the *iso*quinolines when an asymmetric carbon is present. The subsequent alkylation of oxygen and nitrogen offers no problem and is common to many vital processes. It is therefore possible to state with reasonable certainty that plants elaborate 1-substituted *iso*quinolines by condensing 2-dialkoxyarylethylamines (I) or their progenitors with dialkoxyarylacetaldehydes (II) or their progenitors. The ease with which small carbon moieties are bandied about by the living cell does not at present enable us to distinguish between an amino-acid or a pyruvic acid and their decarboxylated derivatives, namely, the corresponding amine or aldehyde respectively. Indeed, if we give credence to the full possible resources of living cells we may find it difficult to distinguish between an amine or its possible progenitors, namely, an aldehyde, ammonia, and a reducing agent.



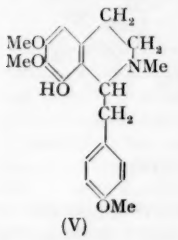
(I) (II) (III) (IV)

That 1-benzyl*iso*quinolines (III) are not ends in themselves and the ultimate product of plant metabolism is not only to be expected *a priori* but is observed in fact. These compounds are genuine 2-arylethylamines and as such should be susceptible to further condensation with aldehydes. There can be little doubt that the biosynthesis of the protoberberines (IV) proceeds *via* the benzyl*iso*quinolines, but the necessary reagent to bring about this condensation has eluded us. That it is not formaldehyde is fairly certain because formaldehyde has never been found in plant cells. There is however another reason why formaldehyde is not the reagent and this is an indirect one. The 1-alkyl*iso*quinolines have either no substituent or a methyl group, so that if formaldehyde were the reagent in one instance it would be expected that acetaldehyde would be the reagent in the second. Alkaloids of type (IV) however have never been found with a methyl group in the new position so that the reagent which brings about the formation of (IV) seems to be one which does not have a naturally occurring homologue, and glyoxylic acid may be such a substance. It has the further merit that it is known to be present in plants. Some interesting problems however emerge at this point. The ring closure to (III) takes place at a position *para* to the hydroxyl group with one exception (where it takes place *ortho* to a hydroxyl group) [6] whereas the ring closure from (III) to (IV) takes place *ortho* to a hydroxyl group with one exception (where it takes place *para*). It seems either that the reagents concerned in the two ring closures are different, or that the mechanisms are different. The second of the exceptions noted above is the alkaloid coreximine in which the *O*-substituents are in the 8 : 9-positions—positions which are assumed when (III) is digested *in vitro* with formaldehyde and hydrochloric acid! There is a benzyl*iso*quinoline (V) which, quite by accident, has given strong positive evidence that benzyl*iso*quinolines are indeed intermediates in the synthesis of protoberberines although the evidence itself is of a negative kind. This benzyl-*iso*quinoline is the only one found in the entire subfamily Fumarioideæ, and it occurs in a plant, *Corydalis aurea*, Willd.,[8] notable for the abundance of protoberberines. Since, however, the possible position of ring closure is neither *ortho* nor *para* to an alkoxyl group, ring closure cannot take place and therefore the alkaloid survives as such.

It should not be assumed however that protoberberines are the final anabolic products of alkaloid biogenesis in spite of their abundance. They afford a number of positions of attack, particularly by oxidizing agents, and these oxidation products can be very interesting. If for instance the hydrogen at position 5 is replaced by a hydroxyl group there results a carbinolamine which, if methylated in ketonic form, gives rise to the protopine type of base (VI). An

[6] A. Pictet and T. Q. Chou, *Ber.*, 1916, **49**, 370.
[7] R. H. F. Manske and W. R. Ashford, *J. Amer. Chem. Soc.*, 1951, **73**, 5144.
[8] R. H. F. Manske, *ibid.*, 1952, **74**, 2864.

alternative, and more pleasing, hypothesis for the formation of (VI) is a preliminary hydroxylation at position 6. This is the position of the hydroxyl group in ophiocarpine [9] as well as in the phthalide*iso*quinolines (VIII), and when such a compound is hydrated and *N*-methylated it gives rise to (VII) which need only lose water to yield (VI). Furthermore, there are two possible ways in which it may be dehydrated, resulting in compounds in which the carbonyl is either at position 5 or at position 6. In the latter case the alkaloid could be cryptocavine and the presence of the two types of ketonic alkaloids in the same plant can scarcely be fortuitous.



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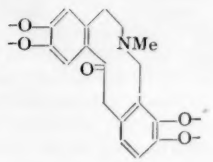

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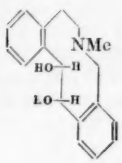

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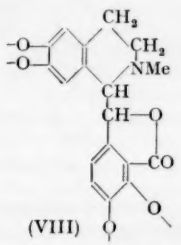
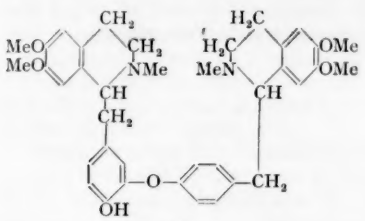


(VIII)

The further oxidation of a 6-hydroxylated protoberberine at position 11, to yield a carboxyl group, and the subsequent methylation of the NH group are sufficient to account for the genesis of the phthalide*iso*quinolines (VIII). It is evident that there are a number of pathways down which the protoberberines may be led and that the nature of the ultimate products is determined by the genetic nature of the plant. The presence of a methyl group at position 6 in a number of protoberberines and protopine-type alkaloids is explicable with some assurance if it is borne in mind that the methyl group in arylacetic acids is potentially already present in tropic and atropic acid, and its introduction in the molecule of (II) before its further assimilation is therefore not without analogy.

While the saga of the protoberberines is not yet exhausted we can return to the benzyl*iso*quinolines. The simplest of their possible transformations, though leading to the most complicated products, is the oxidative coupling of two molecules to yield the so-called biscoclaurine alkaloids, the simplest of which is dauricine. Since the benzyl group has no activated position *ortho* or *para* to a hydroxyl group at which to form a unimolecular condensation product, two molecules must combine if coclaurine is to be changed at all. Plants which elaborate this type of alkaloid (mostly those of the Menispermaceae family) seem to have a one-track mechanism that must form diphenyl ethers at all costs. This process may be repeated until no less than three ether bridges are formed in the one molecule, but the method of forming these bridges is always the same, namely, removal of two hydrogen atoms, one from the phenolic hydroxyl and the other from a position activated by a hydroxyl group.



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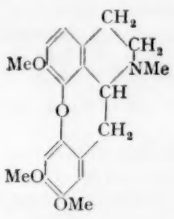

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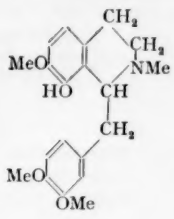


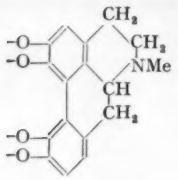
(XI)

A modification of this diphenyl ether formation is the alkaloid cularin (X).[10] This is unique in two respects—it is the only unimolecular diphenyl ether alkaloid and it is the only alkaloid in which the original *iso*quinoline ring closure proceeded *ortho* to an *O*-substituent. There can be no reasonable doubt that the precursor of cularine is the unknown benzyl*iso*quinoline (XI). The spatial arrangements of the atoms in the seven-membered hetero-ring are such that there is very little strain.

Benzyl*iso*quinolines may undergo still another transformation and this is perhaps the

[9] *Idem, Canad. J. Res.*, 1939, **17**, *B*, 51.
[10] *Idem, J. Amer. Chem. Soc.*, 1950, **72**, 55.

simplest of all. If two hydrogen atoms are removed, one from the 8-position and one from either the 2′- or the 6′-position, and the resulting radicals are coupled, two different aporphines (XII) and (XIII) may result. Until some twenty years ago only one type was found in any one plant, but there have been a number of recent examples in which one plant has elaborated both types. It is philosophically more satisfactory to assume one precursor for both types than to assume separate precursors for each.



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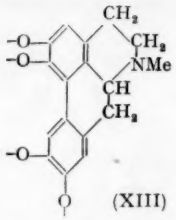

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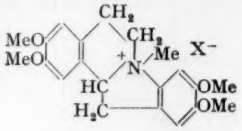
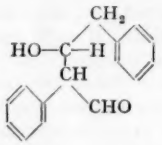


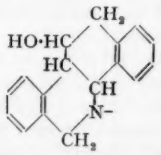
(XIV)

Another and somewhat unexpected dehydrogenation product of a benzyl*iso*quinoline was recently recognised in the alkaloid cryptaustoline (XIV) [11, 12] which was shown to be a partly methylated dehydrolaudanosoline. The oxidative ring closure has brought about quaternization of the nitrogen atom, presumably *via* some type of quinone. This oxidation of laudanosoline and the structure of the product had already been exhaustively studied by Robinson and Sugasawa [13]—tetrachlorobenzoquinone was the oxidizing agent.

To conclude, mention should be made of a group of *iso*quinoline alkaloids which are not derivable from benzyl*iso*quinoline, namely, the 1 : 2-benzophenanthridines. Nevertheless, their precursors are almost certainly identical at least in part with the precursors of the benzyl-*iso*quinolines with which they occur in the same plants. Let two molecules of an aryl-acetaldehyde condense to form the aldol (XV). This by reaction first with ammonia and then

(XV)





(XVI)

with formaldehyde would lead to a compound which by a double ring closure would give the sought-after alkaloids (XVI). The great merit of this scheme is that the hydroxyl group is in the correct place and that one of the possible intermediates is almost certainly analogous to the possible intermediate concerned in the formation of β-phenylnaphthalene from phenyl-acetaldehyde.

[11] J. Ewing, G. K. Hughes, E. Ritchie, and W. C. Taylor, *Nature*, 1952, **169**, 618.
[12] *Idem*, *Austral. J. Chem.*, 1953, **6**, 78.
[13] R. Robinson and S. Sugasawa, *J.*, 1932, 789.

PRESIDENTIAL ADDRESS.

DELIVERED AT THE 113TH ANNIVERSARY MEETING OF THE CHEMICAL SOCIETY AT THE UNIVERSITY, MANCHESTER, ON APRIL 2ND, 1954.

Signs of a New Pathway in Reaction Mechanism and Stereochemistry.

By C. K. INGOLD, D.Sc., F.R.I.C., F.R.S.

LAST year my scientific Address had a somewhat historical tone, and so, to make a change and restore balance, I shall give the present Address a slightly futuristic flavour. Its theme will be that organic chemists interested in the theory of their subject, in the properties of the molecules and in the mechanisms of their reactions, and in how the physical properties bear on the reactions of the molecules, organic chemists, particularly, who would not be content only to fill out the theory of organic chemistry in its present form, but would wish to prepare the ground for a future, more fundamental form, should consider the significance of molecular electronic spectra.

The reason is easily understood. Electron distribution and motion in molecules, as in atoms, is quantised. But because, in general, the stationary states lie energetically far apart, most molecules spend the whole of their lives in one state, the least energised one, which we call the ground, or normal, state. However, all the other states, the so-called excited states, simply by their potential existence, and even if the molecule will never occupy any of them, determine important properties of the normal state, particularly those properties which are of main importance for reactions.

To be specific, the excited states determine that group of properties of the normal state which we summarise in the term " polarisability," using this word, as chemists, in a much more general sense than that which a physicist would seek to express by a coefficient or even a tensor, and including in it the capacity of the system for general and local changes of nuclear and electronic position and motion under every type of deforming force, macrophysical or microchemical.

The nature of excited states determines this " generalised polarisability " of the normal state, because electronic and nuclear position and motion are quantised, and, to this extent, polarisability itself is a quantised property. A deforming force cannot, for example, push the electrons quantally just where it would push them classically. It can only mix with their original distribution and motion a component, depending for magnitude on its intensity, of that particular distribution and motion which belongs to one and/or another of the permitted stationary electronic states. With respect to their control of the polarisability of the occupied normal state, the unoccupied excited states can be pictured as providing certain, sharply defined, more or less steep, openings or roads, into any of which the electrons and nuclei can be partly driven by deforming forces, to an extent depending on the forces, and on how wide the openings are, how steep they are, and in what directions they lie with reference to the forces. (This description has to be broadly interpreted, inasmuch as our metaphorical " roads " provide not only new possible positions, but also new possible motions, for the electrons and nuclei: they are " phase-space " roads.) It should be made clear that a molecule impelled to use these opportunities is still in its normal electronic state, even though, under the deforming forces, that state is modified, having had *dissolved* in it, so to speak, some of the character of one or more of the excited electronic states.

When we reflect that chemical reactions are special consequences of the deformations induced in some molecules by forces due to others, we see at once how important for a physically based theory of chemical reactions must be a knowledge of the excited electronic states of the reacting species.

It is hardly necessary to add that there is much also for the stereochemist, and for the physical chemist, in the study of excited electronic states of molecules. Now that these investigators have discovered so much of what there is to know about the shapes and sizes, and about the mechanical and electrical properties, of most of the simpler typical molecules in their normal states, they should be attracted by the wealth waiting to be won in new knowledge about the morphological and electromechanical properties of excited molecules, new knowledge of a kind whose intrinsic interest, apart from its applications, is their own particular concern.

The excited electronic states of molecules are too highly energised to be thermally accessible. They are photochemically accessible, but are metastable, and with few exceptions, have short lives. We cannot hold a molecule in an excited state, as it holds itself in its normal state, while,

taking our time, we carry it round the well-ordered physico-chemical laboratory, determining its geometrical, mechanical, and electrical characteristics by the various standard techniques for which the equipment is there set up. Physical information about an excited state can only be wrung out of the light which is absorbed or emitted when the molecules are springing between that state and some other, usually the normal state. And thus we are led to the study of electronic spectra, which, as you know, occur mostly in the ultra-violet.

I first got led (one might almost have said " kicked ") into using spectroscopic methods through concern, as an organic chemist, with a normal electronic state : for that, the relevant spectra were vibration-rotation spectra. This was in the early 1930's, when the theory of mesomerism was still on trial, and the most typical of mesomeric molecules, benzene, was being stated by spectroscopists, who commanded the most accurate of known techniques for the study of molecular form, to be devoid of mesomeric symmetry. Eventually this difficulty was resolved, with a reversal of that particular conclusion and the production of a somewhat detailed characterisation of the normal state of benzene, by a method which was then new, though it is commonly used today in the study of molecular structure, namely, the *analysis in parallel* of the spectra of isotopic isomers, our benzene isomers being based on the use of deuterium, which was itself a new chemical discovery at that time.

This satisfactory result suggested that the spectral comparison of isotopic isomers might also help with the characterisation of excited molecular states on the basis of electronic spectra. Here was a field in which new effort of some kind was obviously required. Scores of discrete electronic band spectra had been described, but, except for diatomic molecules, none of them had been analysed sufficiently to allow any single molecular excited state to be given a reasonably precise physical description. By 1948, that is comparatively recently, such a treatment of the first case was completed. It was that of the lowest, singlet, excited state of benzene, the state involved in the very well-known near-ultra-violet spectrum of that molecule. This excited state was fairly fully characterised with respect to its dimensions, internal-force system, and electronic type.

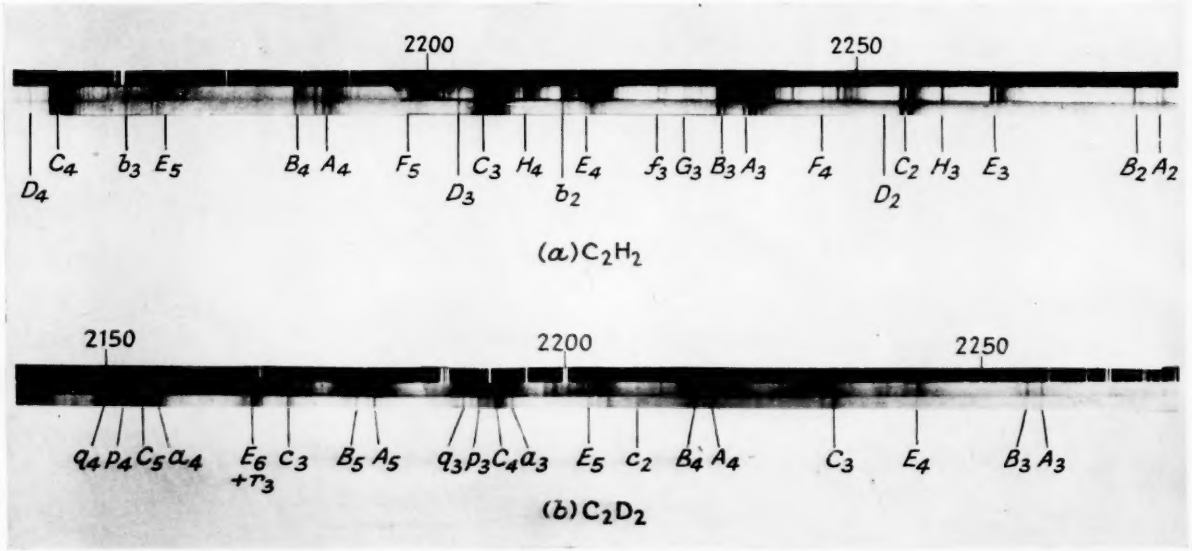
It might seem a little odd that this degree of success in the analysis of a polyatomic electron-spectrum should have been first achieved with a 12-atom molecule, benzene, rather than with some much simpler molecule, such as water or carbon dioxide. But one can suggest a reason. In this lowest, singlet, excited state of benzene, the very stable, aromatic electron-shell is not wholly broken down : it is weakened but preserved, with the result that the excited molecule bears a close general resemblance to the normal molecule, and, in particular, is of exactly the same shape, and very nearly the same size. Such a geometrical similarity of two combining states renders a spectrum simpler and more regular, and very much easier to analyse, than if some drastic reorganisation of the molecular framework had accompanied excitation. But the close similarity also renders this particular excited state much less interesting than some others would be for the interpretation of benzenoid reactions. However, we may reasonably assume that such preservations of basic structure are somewhat exceptional, and that gross changes of structure will often accompany the excitation of valency electrons, which are, after all, the " stanchions " of the structure. I think that one of the reasons why success has come so slowly in the interpretation of polyatomic electron-spectra is that analysis has too often been attempted under the unwarranted preconception that stereochemical form would be approximately preserved. At any rate, it is just when it is not preserved that we have an excited state which could determine a specific kind of polarisability of particular importance for reactions.

To Dr. G. W. King and myself (and the substance of this Address is as much his as mine, though it is only I whom you see) it was clear that the next step in the exploration of lower excited states, as an approach to the interpretation of reactions, should be concerned with a less internally stabilised molecule than benzene. We chose acetylene for its relative simplicity. Its near-ultra-violet absorption spectrum had been described many times, but had never been successfully analysed. Dr. King recorded this spectrum, and the corresponding spectrum of dideuteroacetylene; and he extracted from their combined analysis a fairly complete and accurate account of the excited state, which proved to be widely different in form and constitution from the normal state.

An Address provides an opportunity to explain the principles of such an investigation, without troubling about all the formulæ and numerical particulars that necessarily encumber an original publication. Let us then consider the problem, starting with the experimental observations.

For both the isotopic forms of acetylene, C_2H_2 and C_2D_2, the near ultra-violet band-system, as observed in absorption, starts weakly near 2400 Å, and continues with " ups and downs," but

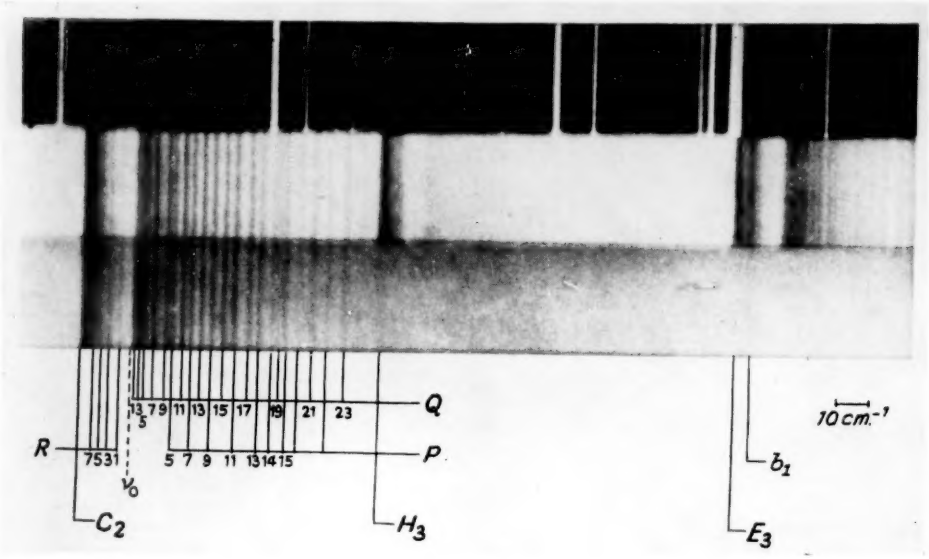
FIG. 1. *Part of the near-ultra-violet absorption spectrum of acetylene and dideuteroacetylene.*



(Top) *Iron-arc comparison spectrum.*
(Central) *Absorption spectrum with gas at* $+20°$.
(Bottom) *Absorption spectrum with gas at* $-80°$.

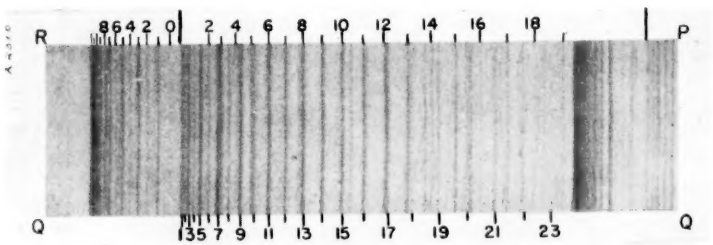
[To face p. 293.

FIG. 2. *Enlargement of absorption spectrum of acetylene between* 2250 *and* 2270 Å, *showing, in particular, the rotational structure of band* C_2.



(Top) *Iron-arc comparison spectrum.*
(Central) *Absorption spectrum with gas at* $+20°$.
(Bottom) *Absorption spectrum with gas at* $-80°$.

FIG. 3. *Enlargement of the absorption spectrum of acetylene between* 2310 *and* 2317 Å, *as observed in the fourth order of a* 21*-foot grating, showing, in particular, the rotational structure of band* C_1.



Note the alternation of line intensities, which is due to the spin of the hydrogen nuclei, and the consequent co-existence of ortho- and para-forms of acetylene. This photograph was very kindly presented by Dr. G. Herzberg and Dr. K. K. Innes for illustration of this Address.

generally increasing strength, to 2100 Å, where it becomes overlapped by another band-system belonging mainly to the vacuum-ultra-violet. Up to the point of overlap, the spectrum of either acetylene contains rather less than 100 measurable bands, but without any obvious regularity of arrangement, as will be clear from the segments of spectra, each for two temperatures, shown in Fig. 1. Now the normal acetylene molecule is linear. If the excited state were also linear, we should expect to see, just as for diatomic molecules, a simple repeat-pattern of regularly spaced bands. Here then is a first hint that the upper electronic state is not linear.

Of course, the fact that the spectrum consists of many bands indicates the presence of various numbers of quanta of one or more vibrations in either or both of the combining states. We can distinguish to which electronic states these vibrational quanta belong by a study of the temperature dependence of band intensity. Some bands, for instance those labelled *C*, are not weakened by cooling the gas. Others, such as those labelled *A* and *B*, are weakened moderately. Others, again, such as those termed *E*, are weakened more. Yet others, such as those called *F*, are weakened more still. Two further classes of bands can be observed, which, in successive degrees, are even more temperature-sensitive. The half-dozen of classes into which the bands fall with respect to their temperature-sensitivity distinguish the different vibrational levels of the normal electronic state, from which, in absorption, the transitions start: those levels with more vibrational energy are more strongly depopulated by cooling, with consequent weakening of the bands. This consideration allows us to sort out the vibrations, whose frequencies we shall deduce from the band separations, into those which belong to the normal state, and those which belong to the excited state.

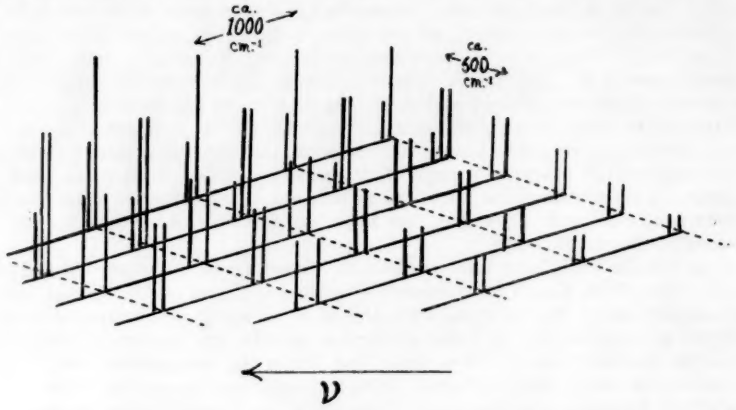
Let us now make a similarly brief, preliminary inspection of the rotational fine structure of the bands. One of Dr. King's enlargements of a band is shown in Fig. 2. At first sight, the pattern looks like one of the two standard patterns, which are given by diatomic molecules, and are expected to be given by all linear molecules, namely, the pattern formed when, in the transition, the electrons oscillate, not along, but across the internuclear line: there is an *R* branch running one way, and overlapping *Q* and *P* branches running the other. Through the kindness of Dr. Herzberg and Dr. Innes, I can show you a much better photograph (Fig. 3), obtained by them with Dr. Herzberg's much larger spectrograph. However, the pattern is not quite as simple as it looks; for when we measure the line positions, and compare them with the standard formulæ for linear molecules, we find that, relatively to the lines of the *P* and *R* branches, which are consistent among themselves, the lines of the *Q* branch are too widely spread; so that for the total band, we have to assume two spacing constants, instead of only one. These spacing constants depend on the large moments of inertia of the molecule; and so we have to conclude that, corresponding to the two large, equal, moments of inertia of linear normal acetylene, there must be two large, but unequal, moments of inertia in excited acetylene, which therefore cannot be linear.

Let us look a second time, and now more closely, at the coarse structure of the spectrum. In seeking to understand such a situation, it is better at first to consider it semiquantitatively, indeed, almost qualitatively, without troubling about precise values: the quantitative fit will come by itself when the right qualitative idea is found. First, we pick out the bands of the temperature-independent class: we find that they form a series of small clusters, roughly 1000 cm.$^{-1}$ apart in C_2H_2, and 800 cm.$^{-1}$ in C_2D_2. Proceeding to the next more temperature-sensitive class, we find that these bands form a similar progression of clusters, again about 1000 cm.$^{-1}$ apart in C_2H_2 and 800 cm.$^{-1}$ in C_2D_2, but shifted bodily to lower frequencies by roughly 600 cm.$^{-1}$ in C_2H_2 and 500 cm.$^{-1}$ in C_2D_2. All these numbers have to be rough, because each band-cluster contains two or three bands, spread over a range of the order of 100 cm.$^{-1}$; and, as the clusters are not all alike, we do not know from what precise point within each cluster to measure the separation of the clusters. The next more temperature-sensitive class is again similar, and shows a similar, further shift by about 600 or 500 cm.$^{-1}$ to lower frequencies; and so on, throughout the remaining temperature classes. Thus, when we take an "aeroplane view," instead of a "ground-level view" of the spectrum, we see (Fig. 4) that the bands do have a pattern. Actually this "two-dimensional pattern," as we may call it, is repeated, more weakly, a second and a third time, with displacements to higher frequencies by other, unrelated intervals, which will be mentioned again later, the three two-dimensional patterns overlapping.

Apart from the complication of having a band-cluster, instead of a single-band, at every point in the two-dimensional pattern, the meaning of this pattern is clear. The interval of about 600 cm.$^{-1}$ in C_2H_2 between successive temperature classes of bands must, as I have explained, be a vibration frequency of the normal state, and the interval of about 1000 cm.$^{-1}$ between successive band-clusters of a temperature class, must be a vibration frequency of the excited state.

Thus the energy diagram is as shown in Fig. 5. We conclude that there is a vibration, of frequency about 600 cm.$^{-1}$ in normal acetylene, and about 1000 cm.$^{-1}$ in excited acetylene, which undergoes *unrestricted quantum changes* during the conversion of one state into the other. Now the Franck–Condon principle teaches that the only vibrations which can appear thus freely in

FIG. 4. *Schematic representation of the "two-dimensional" pattern of bands, which recurs in the first ultra-violet band-system of* C_2H_2 *and of* C_2D_2. *The full-lines join bands whose intensities have the same temperature coefficient. The temperature dependence of band intensity increases along the broken lines towards the "fore-ground." Rotation is responsible for the appearance of a small cluster of bands, instead of one band, at each "lattice point" of the two-dimensional pattern.*



an electronic transition are those which *have inevitably* to be aroused in order to convert the shape of the molecule in one state into its shape in the other. Hence, if we can identify the vibration responsible for the pattern, we shall know how the two shapes differ. This identification is easy: we know from infra-red and Raman spectra the normal-state frequencies of all the five vibrations of acetylene, and of dideuteroacetylene. From the list of them (Fig. 6), we

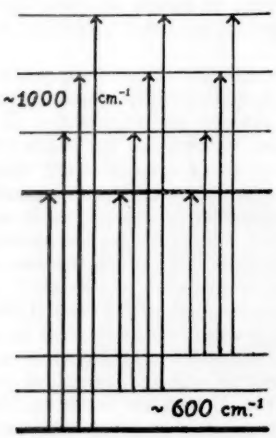


FIG. 5. *Energy diagram corresponding to the two-dimensional pattern of band clusters. The thick horizontal lines represent the energies of the normal and excited electronic states without vibration, whilst the thin horizontal lines indicate the energies of these states when in possession of one, two, etc., quanta of the vibration responsible for the pattern. The vibrational spacing is much magnified, relatively to the electronic spacing. The vibration concerned is the chief of those needed to interconvert the shapes of the two states, a* trans*-bending vibration of the normal state, and a straightening-bending vibration of the excited state. The indicated transitions correspond to the first four band clusters of each of the first three temperature classes.*

see that the only vibration which could conceivably be made responsible for the normal-state frequencies, found in the ultra-violet spectrum, of about 600 cm.$^{-1}$ in C_2H_2 and about 500 cm.$^{-1}$ in C_2D_2, is the *trans*-bending vibration, the fundamental frequencies (that is, the frequencies of the first quantum) of which are actually 613 cm.$^{-1}$ in C_2H_2 and 511 cm.$^{-1}$ in C_2D_2. Therefore the first excited electronic state of acetylene must be a *trans*-bent state.

From this point the way is all down-hill to a quantitative answer. We look a second time,

and more closely now, at the rotational fine structure. We bear in mind that the *trans*-bent model shows qualitatively that, because of the relative lightness of hydrogen, there must be one axis of uniquely small inertia (axis *a* in Fig. 7), round which rotation will be singularly rapid, and its quanta singularly large. The rotations about the two axes of large inertia (axes *b* and *c* in Fig. 7) will be slow, and their quanta much smaller. The two orders of magnitude of the rotational quanta will cause the lines of a complete band to separate into several bunches, each

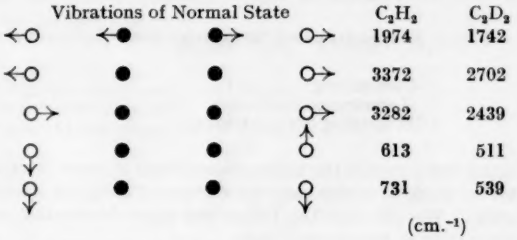


FIG. 6. *Fundamental vibration frequencies of the normal state of acetylene and dideuteroacetylene. The frequencies show that no vibration other than the* trans-*bending vibration (second from bottom) could be responsible for the two-dimensional pattern of bands found in the ultra-violet absorption spectrum.*

of which, though constitutionally only part of the band, will have all the appearance of being itself a band, with its *P*, *Q*, and *R* branches. This is the explanation of what we called the " band clusters." The separations of the bands of a cluster measure the large rotational quanta,

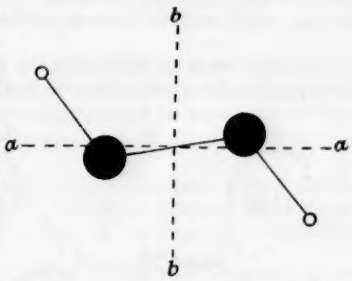


FIG. 7. *Model of metastable* trans-*bent acetylene showing the position of the axes of inertia. Only axes a and b are shown: axis c is perpendicular to both, and thus perpendicular to the plane of the molecule. The moment of inertia about axis a is much smaller than are the moments of inertia about axes b and c, so that the frequencies and quanta of rotation about a are much larger than those about b and c. The co-existence of large and small rotational quanta causes the lines of a complete band to separate into distinct bunches, each of which looks like a band, so that we see a " cluster of bands" where a single band might have been expected. For* C_2H_2 *the determined values of the moments of inertia are* $10^{40}I_a = 2{\cdot}24$, $10^{40}I_b = 24{\cdot}83$, $10^{40}I_c = 27{\cdot}09$ *g.-cm.*^{2}. *That the sum of the first two equals the third (to within the accuracy of their determination) shows that the molecule is planar.*

while the separations of the lines of the *P* and *R* branches, on the one hand, and of the *Q* branch, on the other, measure the two sorts of small quanta. These values give us the three moments of inertia of the excited molecule, and such data for both C_2H_2 and C_2D_2 permit a quantitative determination of molecular form. The excited molecule is thus found to be accurately planar, *trans*-bent, and centro-symmetrical. The bond lengths and angles are shown in Table 1, where they are compared with the known geometrical data of the normal molecule. We see that the excitation has produced a gross angular change from 180° to 120°, and also a considerable elongation of the C–C bond, as well as some elongation of the two C–H bonds.

TABLE 1. *Stereochemical parameters of normal and excited acetylene*

	Normal	Excited
C–C bond length (Å)	1·208	1·385
C–H bond length (Å)	1·058	1·08
CCH bond angle	180·0°	120·2°

Let us now pass from the geometrical to the mechanical characteristics of the excited state. One result of our rotational analysis is that we now know the point within each band cluster from which to measure its separation from other clusters, without including any rotational energy in the measurement of vibrational energy. Measured in this way, the *trans*-bending frequencies of the normal state agree exactly with known values, for instance, with 613 and 511 cm.$^{-1}$ for the first quantum in C_2H_2 and C_2D_2, respectively. Similarly, we can get the exact frequencies of the related bending vibration of the excited state. We have just noticed that in the excitation, the C–C and C–H bonds become elongated; and this means that, in addition to the strong bending motion, a certain amount of the C–C stretching vibration, and a little of the symmetrical C–H stretching vibration, will be needed in order to interconvert the structures.

Now I mentioned that the two-dimensional pattern of bands, which itself is due essentially to the involvement of many quanta of the bending vibration, is more weakly repeated in the spectrum, with displacements by single quanta of two other vibrations of the excited state. These displacements give us the C–C, and the symmetrical C–H stretching frequencies of the excited state; and, knowing them, as well as the bending frequency, for both C_2H_2 and C_2D_2, we can calculate the internal force-system of the excited molecule. The fundamental frequencies of excited C_2H_2 and C_2D_2, thus deduced, are in Table 2. The elastic constants of the excited

TABLE 2. *Fundamental frequencies (cm.$^{-1}$) of excited acetylene and excited dideuteroacetylene.*

	C_2H_2	C_2D_2
C–C stretching	1380	1310
C–H stretching (in phase)	3000	2215
CCH bending (straightening)	1049	844

state, computed in the conventional form of bond-stretching bond-angle-bending force-constants, are in Table 3, where they are compared with the known corresponding constants of the normal state. We see that the bonds are easier to stretch, but much harder to bend, in the excited state than in the normal state.

TABLE 3. *Elastic constants of normal and excited acetylene.*

	Normal	Excited
C–C stretching (dyne/cm.)	$15{\cdot}8 \times 10^5$	$7{\cdot}2 \times 10^5$
C–H stretching (dyne/cm.)	$6{\cdot}0 \times 10^5$	$5{\cdot}1 \times 10^5$
CCH bending (dyne-cm./radian)	$1{\cdot}5 \times 10^{-12}$	$8{\cdot}5 \times 10^{-12}$

Finally, we must determine the electronic structure of the excited state. The fact that its bond angles have been reduced to 120°, shows already that the σ-bonding (or σ-hybridisation)

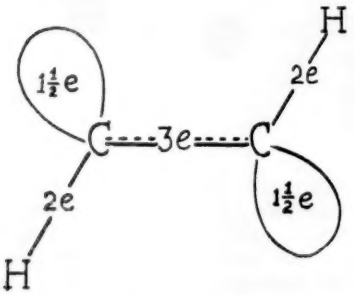


FIG. 8. *Schematic representation of the stereochemistry and electronic structure of the first excited state of acetylene. The stereochemistry is that of ethylene with two* trans*-related hydrogen atoms removed. The* C–C *bond is a three-electron bond of the constitution* $\{(2sp^2)\sigma\}^2\{2p\pi\}$, *as in normal benzene, while the* C–H *bonds are two-electron bonds,* $\{(C2sp^2)(H1s)\sigma\}^2$, *as in either normal ethylene or normal benzene. The remaining valency-shell electrons, assigned to the number* 1·5 *to each carbon atom, are in* $\{2sp^2\}$ *orbitals, and are essentially unshared; but each carbon nucleus has a little concern with the unshared electrons of the other carbon atom, and to this extent "completes its octet."*

has changed completely from acetylene-type to ethylene- or benzene-type. It follows that, one of the two π-orbitals of the original triple bond must have been broken into two unshared-electron orbitals. These, after they have accommodated the two electrons of the broken orbital, still have two vacant places, and therefore more than enough room for an electron excited out of the remaining π-orbital. That this is indeed the mechanism by which the molecule achieves its energetically lowest electronic excitation is shown by the band forms. Their three-branch character requires that, in the excitation, the electrons oscillate across the line of the nuclei in the normal state, and across the plane of the nuclei in the excited state; and this in turn means that, in the excited state, one electron has been lifted out of the π-orbital, for which the molecular plane is a nodal plane, and has gone into a σ-type of orbital, for which that plane is not a nodal plane. So we arrive at the picture shown in Fig. 8 of the excited molecule, with ethylene-type hybridisation, but with a 3-electron C–C bond, *trans*-hydrogen atoms, and 1½ unshared electrons on each carbon atom in *trans*-positions.

This is an excited molecule: the simplest normal molecule, whose C–C and C–H bonds both have electronic constitutions like those of the bonds of excited acetylene, is normal benzene. It is therefore of interest to compare the geometrical and mechanical constants of normal benzene and excited acetylene. As Table 4 shows, these constants are almost the same—indeed most of them are the same to within the accuracy of the figures. Thus the *trans*-bent state of acetylene, except that it is the *trans*- rather than the *cis*-stereoisomer, is quite similar to one-third of the

benzene ring. I have little doubt that the spectrum of the *cis*-bent state of acetylene is present among the band-systems which can be seen further out in the ultra-violet. This *cis*-bent state should be very like indeed to one-third of the benzene ring.

I have described the discovery of metastable *trans*-bent acetylene at some length, because it is as yet the only quantitatively characterised state of major interest in this still embryonic line

TABLE 4. *Comparison of geometrical and mechanical constants of normal benzene with those of excited acetylene*

	Normal C_6H_6	Excited C_2H_2
Dimensions :		
C–C bond length (Å)	1·39	1·385
C–H bond length (Å)	1·08	1·08
CCH bond angle	120·0°	120·2°
Force constants :		
C–C stretching (dyne/cm.)	$7·6 \times 10^5$	$7·2 \times 10^5$
C–H stretching (dyne/cm.)	$5·1 \times 10^5$	$5·0 \times 10^5$
CCH bending (dyne-cm./radian)	$8·0 \times 10^{-12}$	$8·5 \times 10^{-12}$

of enquiry into the factors of molecular polarisability, in the chemically generalised sense of that term. Since the *trans*-bent state is the lowest excited state, we may infer that, on the approach of an electrophilic reagent to a normal acetylene molecule, the latter will display a strong tendency to throw up active electrons in *trans*-positions : in terms of our metaphor, this particular " road " is not very steep. And, although much detail remains to be filled in, we may connect this expected tendency with the known general importance of *trans*-additions to acetylenic compounds.

On the other hand, the acetylenic bond also must possess a form of polarisability which allows it to produce active *cis*-positions, as we know it does in additions, such as Diels–Alder synthesis, in which *trans*-reaction is sterically precluded. Such polarisability must be controlled by the *cis*-bent excited state; and indeed this consideration is the main reason for postulating the existence of a *cis*-bent metastable form of acetylene.

I suggested that the *cis*-bent state of acetylene should be very like one-third of the benzene ring. Conversely, if we could eliminate two *ortho*-hydrogen atoms from benzene, the residue should be very like the *cis*-bent state of acetylene. This, in essence, is the explanation recently

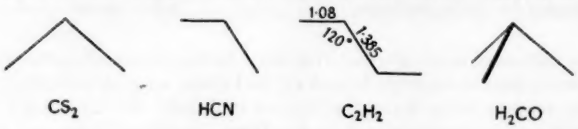
FIG. 9. *Illustrating the proof given by J. D. Roberts and his co-workers that the basic amination of an aryl halide involves a " benzyne " intermediate. The carbon atom marked with a spot was labelled with* ^{14}C, *and it was found that the amino-group went equally into this position and into the* ortho-*position. (The formal triple bond may be regarded as " opened," as it would be in the* cis-*stereoisomer of* trans-*bent acetylene.)*

given, with strong experimental support, by Professor J. D. Roberts of certain nucleophilic substitutions in aryl halides, having *ortho*-hydrogen, by amide ions, which, as very strong bases, could be supposed to dehydrohalogenate the aromatic substance and are in fact found to enter partly into the position of the displaced halogen and partly, instead, into the *ortho*-position. He has shown this convincingly for chlorobenzene itself by labelling with ^{14}C, as I have labelled with a spot (Fig. 9), one of what would otherwise become, on this theory, two completely equivalent ring positions, and obtaining, as the theory requires, just 50% of substitution in each of the two positions.

The study of the transitions and polarisability of acetylene has only begun : other excited states await discovery; and the relevant polarisability terms must be computed. However, the investigation oultined indicates a path which can probably be followed a long way. In a recent, highly suggestive, theoretical discussion Dr. Walsh has adduced detailed arguments to the effect that gross changes of form and constitution should be the rule, not the exception, in valency-shell excitations. And some evidence of the truth of this can be found in previous incomplete analyses of the spectra of several molecules, besides acetylene, most of them prototypes of large classes of organic molecules. As early as 1938, Dr. Price and Miss Simpson

suggested that some of the excited states of carbon disulphide must be bent, and in 1941 Professor Mulliken made the same suggestion for the lowest excited state in particular : the simple point is that the high complexity of its band system would be unaccountable otherwise. I have Dr. Herzberg's permission to mention that he and Dr. Innes have recently found that the first excited state of hydrogen cyanide is bent, and that they are now engaged in a more quantitative evaluation of this state. There is a large literature of the first electronic band-system of formaldehyde; and, though no final analysis has yet been presented, Dr. Walsh pointed out, in the course of the discussion to which I referred, that the two most reasonable outlines of interpretation both involve the conclusion that the excited state is pyramidal. If, to this collection of cases, we add the one completed study, that of acetylene, we obtain an overall picture (Fig. 10), which suggests that the line of investigation illustrated has a future. Indeed, I take these

FIG. 10. *Survey of the stereochemistry of some excited molecular states (qualitative except for* C_2H_2*), as derived by partial or complete analysis of ultra-violet band-systems :* CS_2 *by W. C. Price and D. M. Simpson* (1938); *and R. S. Mulliken* (1941); HCN *by G. Herzberg and K. K. Innes (personal communication);* C_2H_2 *by G. W. King and C. K. Ingold* (1952; 1953); H_2CO *by A. D. Walsh* (1953).



various observations and conclusions to be straws showing the way the wind blows—to be portents of what will one day be a large new field of stereochemistry, that of excited states, and a field which will bear an important part of the foundations of a better theory than we have now, of the steric and electronic mechanism of organic reactions.

ONE HUNDRED AND THIRTEENTH ANNUAL GENERAL MEETING.

THE One Hundred and Thirteenth Annual General Meeting of the Chemical Society was held on Friday, April 2nd, 1954, in the Large Chemistry Lecture Theatre, the University, Manchester. The President took the Chair at 9.45 a.m. and called upon Dr. L. E. Sutton, Honorary Secretary, to read the notice convening the meeting.

The notice having been read, the President called upon Professor E. D. Hughes, Honorary Secretary, to present the Report of Council. Professor Hughes pointed to the continued growth of the Society during the past year but emphasised that the Society was also losing members more rapidly. This was a matter of some concern to the Council and was one of the main reasons for the proposal to adopt the reduced rate of basic subscription to be proposed later. Referring to the Society's publications, Professor Hughes remarked that more papers were now being received for publication in the *Journal* and it appeared that the reduction in size of the *Journal* of 1953 would not be repeated. As had already been announced the Bureau of Abstracts would be closed down when all the issues, including Indexes, for 1953, had been completed. This failure of *British Abstracts* had arisen entirely for financial reasons and was described fully in the Report. Professor Hughes referred briefly to the measures which had been taken to replace in some way the Abstracts and described the publication by the Society at short notice of *Current Chemical Papers*. This new publication had been favourably received by the Fellowship.

In conclusion, Professor Hughes expressed the thanks of the Society to all those who had assisted in its work during the past year. In particular he mentioned those who had acted as referees for papers submitted to the *Journal*, and contributors to the *Annual Reports* and *Quarterly Reviews*, as well as those who had served on the various committees of the Society or acted as Local Representatives. Thanks were also due to the many donors of books presented to the Library. Professor Hughes also referred to the permanent staff of the Society and thanked them for their work during the past year.

The President then referred to the illness of Sir Wallace Akers, the retiring Honorary Treasurer, and expressed the Society's appreciation of the great service he had rendered during his six years of office. That period had been one of exceptional financial difficulty, and the fact that the Society had emerged with its finances unimpaired was due in no small measure to the untiring energies of its Honorary Treasurer. Large contributions had been forthcoming to assist in the Society's work but at the same time steps had been taken to ensure that the Society should, so far as possible, become independent of outside grants.

In the absence of the Honorary Treasurer, the financial section of the Report and the Accounts were presented by Professor H. Burton, Senior Honorary Secretary. The Accounts must be considered satisfactory in view of the increased yield from Fellows' subscriptions and from the sale of publications. Expenditure on the *Journal*, owing to its smaller size, was less than in 1952 and this had enabled the Society to place certain sums to reserve. It was noted that, had it not been for payments to the Bureau of Abstracts, the Society would not have required any grants from outside sources during the year.

After discussion the President moved that the Report of Council and the Accounts be adopted by the meeting. This proposal was seconded by Dr. Sutton and was unanimously accepted.

The President then announced the following elections to vacancies on the Council :

President :

Professor W. Wardlaw.

Vice-Presidents :

Professor E. R. H. Jones. Professor R. P. Linstead. Professor H. W. Melville.

Honorary Treasurer :

Mr. M. W. Perrin.

Elected Ordinary Members of Council :

Constituency I :

Dr. E. A. Braude.
Dr. H. M. N. H. Irving.

Constituency II :

Dr. E. J. Bourne.
Professor H. D. Springall.

Constituency III :

Professor H. N. Rydon.

Constituency IV :

Dr. C. C. Addison.

Constituency V :

Professor J. M. Robertson.

Constituency VI :

Dr. V. C. Barry.

The President then referred to certain proposals, submitted by the Council, for the modification of the Bye-Laws. A major reason for the changes was the desire of the Council to introduce a form of basic subscription carrying no entitlement to publications. If this proposal was carried the necessary resolutions would be submitted to an Extraordinary General Meeting to follow the present meeting. Other changes had been made in order to bring the Bye-Laws of the Society into conformity with current practice. These reasons had been described fully in a circular letter addressed to all Fellows. One further modification proposed concerned the ownership of copyright of papers contained in the *Journal*. The Council had considered it desirable and in the interests of the Fellows that the Society should have power to acquire the copyright. This would assist those wishing to copy from the *Journal* who might under the present Bye-Laws be seriously hampered if the ownership of copyright was uncertain or if the owner was not accessible. In addition, the Society would in all probability wish to make arrangements for the re-issue by a commercial publisher of certain volumes of the *Journal*. Such an arrangement and also the issue of a micro-film edition would be greatly facilitated if the Society had power to acquire the copyright.

The President then referred to the suggestion contained in the circular letter addressed to all Fellows that it was necessary for the Society to own copyright because it had subscribed to the Royal Society's " Fair Copying Declaration." He regretted that this was misleading in so far as the Declaration was merely a statement of what, in the opinion of the signatories, represented fair copying. It might be, however, that the Society's opinion on this matter would carry more weight if in fact it was the owner of the copyright.

It had been represented to the Council that the wording of the proposed Bye-Law might appear to restrict an individual author from copying his own work. The Council certainly did not wish to hamper authors or even to appear to do so, and an amendment had been proposed which he considered would protect authors' rights. This amendment would be incorporated in the formal resolution for the adoption of the new Bye-Laws when it was put to the meeting.

There was a discussion on the new Bye-Laws and on the proposed amendment. Dr. E. Rothstein, speaking on behalf of a number of Fellows in Leeds, asked for a further explanation of several points and proposed as an additional amendment that the words " of publication " be inserted after the word " form " in the third line of Bye-Law 79 (i) (*b*) This further amendment was seconded and was put to the meeting. It was defeated by a large majority, greatly exceeding two-thirds of those Fellows present and voting.

After further discussion, the following amended resolution proposed by the President and seconded by Dr. Sutton was put to the meeting and was carried *nem. con.*

> " That the draft Bye-Laws submitted to the meeting, of which a print has been signed by the Chairman for the purpose of identification, be and they hereby are adopted as the Bye-Laws of the Society in place of the existing Bye-Laws. Subject to the proposed new Bye-Laws being amended by the addition at the end of Bye-Law 79 (i) (*b*) of the words ' The Council shall not refuse any reasonable request from an author to reproduce his own work elsewhere in the whole or in part.' "

On the motion of Dr. L. E. Sutton, seconded by Professor H. Burton, Messrs. W. B. Keen and Co., Finsbury Circus House, London, E.C.2, were appointed as Auditors for the year 1954.

The President then declared the Annual General Meeting terminated.

EXTRAORDINARY GENERAL MEETING.

The President called upon Dr. L. E. Sutton to read the notice convening the meeting and to propose the following resolution :

> " That, subject to the adoption of the draft Bye-Laws, submitted to the One Hundred and Thirteenth Annual General Meeting, as the Bye-Laws of the Society, the Annual Subscription of a Fellow of the Society shall, from January 1st, 1955, be reduced to Two Guineas."

The resolution, having been proposed by Dr. Sutton and seconded by Professor Burton, was, after a brief discussion, put to the meeting and was carried unanimously.

On the conclusion of the meeting a vote of thanks to the President, Officers, Council, and Local Representatives of the Society was proposed by Professor E. R. H. Jones, seconded by Mr. J. D. Rose, and carried with acclamation. The proceedings then terminated and were resumed at 11 a.m. when the President delivered his Presidential Address, " Signs of a New Pathway in Reaction Mechanism and Stereochemistry " (*J.*, 1954, 2991).

REPORT OF COUNCIL FOR 1953.

I. PATRON.

An Address of loyalty and congratulation was submitted, on behalf of the President, Council, and Fellows of the Society, to H.M. Queen Elizabeth II, Patron of the Society, on the occasion of her Coronation on June 2nd.

II. FELLOWSHIP.

1. *General.* Fellowship changes in 1953, and in previous years, are given in the following table:

TABLE 1.

	1949	1950	1951	1952	1953
Number of Fellows on January 1st	7873	8195	8353	8616	9063
Additions:					
Elections	675	749	700	947	790
Reinstatements	26	29	25	34	29
Miscellaneous	—	1	—	1	—
	— 701	— 779	— 725	— 982	— 819
Deductions:					
Deaths	60	66	62	65	58
Resignations	210	267	273	341	467
Removals	109	181	127	128	106
Miscellaneous	—	107	—	1	2
	— 379	— 621	— 462	— 535	— 633
Net increase in year	322	158	263	447	186

The Fellowship at December 31st (9249) is the largest in the history of the Society, and it is gratifying to record that the Fellowship has increased for thirteen consecutive years. Some concern must be expressed, however, at the increasing number of resignations reported during the year. The average Fellowship-duration of those ceasing to belong to the Society is now only 8·1 years compared with 12·3 years in 1938.

The number of Fellows participating in the Joint Subscription Scheme sponsored by the Chemical Council was 4407, a decrease of 430 during the year.

2. *Honours.* The Council has conveyed the congratulations of the Society to the following whose names appeared in the Honours Lists during 1953:

K.B.E.

Hugh Stott Taylor (Honorary Fellow).

C.B.

Robert Spence.

C.B.E.

Donald Neil McArthur.
Reginald Bradbury Southall.

The Council has also congratulated the following to whom awards were announced during the year:

Nobel Laureate.

Professor H. A. Krebs.

Priestley Medal of The American Chemical Society.

Sir Robert Robinson.

3. *Deaths.* The Council records with deep regret the death, during the year, of three distinguished Honorary Fellows of the Society—Wilder Dwight Bancroft, Claude Silbert Hudson, and Nikolai Dimetrievich Zelinsky. The Council also regrets to report the death of Samuel Smiles, who served the Society as Secretary (1912–20) and as Vice-President (1920—23).

III. PUBLICATIONS.

1. *Journal.* During 1953, 946 scientific communications were received and 866 published. In comparison with 1952 (1046 received, 1000 published), these figures represent decreases of 9·6 and 13·4% respectively. During 1953, 22 communications were declined and 30 were withdrawn. Table 2 shows some comparative figures.

TABLE 2.

	1938	1948	1951	1952	1953
Papers and Notes received.....	507	548	910	1046	946
Less rejected or withdrawn	11	17	71	59	52
	496	531	839	987	894
Papers and Notes published	404	511	778	1000	866
No. of pages (Papers and Notes) ...	1917 *	2203	3368	4901 *	4028 *
No. of pages (total, excluding Index Volume)	2120 *	2330	3514	5056 *	4200 *
Average no. of pages per communication	4·75 *	4·35	4·33	4·90 *	4·65 *

* Pre-war sizes of type.

Simple comparison of total receipts during 1952 and 1953 is misleading. There was a peak in the third quarter of 1952, and a great drop in the fourth quarter of 1952; then during the last three quarters of 1953 the rate of receipt gradually increased. Consequently the *Journal* for 1954 is expected to be more comparable in size with that of 1952 (5056 pp.) than with that of 1953 (4200 pp.).

The *Journal* for 1953 contained 889 items made up as shown in Table 3, where some comparative figures are also given. Table 4 shows that the distribution of papers between the three classes varies only slightly, although the percentage of Physical Organic papers has fallen since 1949, while that of General, Physical, and Inorganic has steadily increased. The upward trend in the proportion of Notes has been maintained, although the proportion still remains fairly low.

TABLE 3.

Numbers of items in the Journal.

	1938	1948	1951	1952	1953
Papers (General, Physical, and Inorganic)	102	124	131	194	180
,, (Physical Organic)	—	16 *	100	134	93
,, (Organic)	275	326	462	556	492
Notes	27	45	85	116	101
Lectures and Addresses	9	5	3	6	6
Obituary Notices	37	17	9	21	14
Annual General Meeting	1	2	1	2	1
Editorial Nomenclature Report ...	—	—	1	1	1
Report by Symbols Committee of the Royal Society	—	—	1	—	—
I.U.P.A.C. List of Atomic Weights	1	—	1	—	1
,, Report of Commission of Nomenclature of Inorganic Chemistry	—	—	1	—	—
	452	535	795	1030	889

* Class first introduced in the *Journal* for December 1948.

TABLE 4.

Percentage distribution in the Journal.

	1938	1948	1949	1950	1951	1952	1953
Papers (General, Physical, and Inorganic)	25·2	20·3	16·9	18·4	16·8	19·4	20·8
,, (Physical Organic)	—	3·1	14·4	13·8	12·8	13·4	10·8
,, (Organic)	74·8	63·8	60·9	58·7	59·4	55·6	56·7
Notes	6·8	8·8	7·8	9·1	10·9	11·6	11·7

Contributions from industrial laboratories and industrial research organisations published during 1953 totalled 100, including 10 published jointly with academic institutions and 1 jointly with a Government organisation; this represents 11·6% of the total. Contributions from Government sources totalled 41, including 10 jointly with academic institutions and 1 jointly with an industrial organisation. Communications from overseas published during 1953 numbered 140 (16·2%) (1951, 15·6%; 1952, 15·7%). Their proportion has, therefore, increased slightly. Of these, 4 were published jointly with British laboratories (given in parentheses in Table 5).

TABLE 5.

	1948	1951	1952	1953
Australia	13	38(1)	62(1)	50
British Colonies and Protectorates	—	4(1)	6(3)	5(1)
Canada	2	1	2(1)	2
Egypt	15	22	12	8
France	2	10	10	7
Hungary	6	1	3	7
India	3	3	3(1)	6
Irish Republic	—	5	4	5
Israel	2	7	10(2)	20
New Zealand	14	5	18	12(1)
South Africa	1	10	14(1)	7
U.S.A.	2	13(7)	8(3)	7(1)
Miscellaneous	7	2(1)	5	4(1)
	67	121(10)	157(12)	140(4)

The number of communications received during 1953 less the number rejected or withdrawn was 894; the number published during the year was 866. An analysis has shown that the normal time, to the nearest week, between receipt of communications and their publication (taken as the last day of the month) is 21—22 weeks, which is about 1 week slower than in 1952. Communications for which diagrams or figures are required take about four weeks longer to appear than those for which they are not required. The fastest time of publication during the year was 13 weeks. The fact that papers accepted exceed papers published by 28 is due partly to the rise in the rate of receipt and partly to the slower publication rate; there was slight congestion at the printers during the late summer, which has since been overcome.

2. *Annual Reports on the Progress of Chemistry for* 1952 (*Volume XLIX*). These were issued in July 1953 and contained 381 pages (428 in 1952, and 490 in 1951).

3. *Quarterly Reviews.* Volume VII (1953) contained 16 articles occupying 443 pages (Volume VI, 15 articles, 398 pages).

4. *British Abstracts.* The Chemical Society has been engaged in the publication of *Abstracts* since 1841. From 1924 this responsibility was entrusted to the Bureau of Abstracts, a body set up to co-ordinate abstracting on behalf of the Chemical Society and the Society of Chemical Industry. In 1945 the Bureau was incorporated as a company limited by guarantee and not having a share capital. Later other societies interested mainly in the physiological, biochemical, or analytical aspects of chemistry became associated with the Bureau under separate agreements.

From the financial aspect the publication of *Abstracts* has never been profitable, and the Society has for many years been obliged to subsidise its *Abstracts* at the expense of other activities or to seek assistance from outside sources. During the past five years the position became steadily worse. The large increase in scientific work published throughout the world was coupled with a very considerable rise in printing costs and a decrease in the number of individuals able to afford to purchase personal copies of *Abstracts* at an economic price.

The Council recognises that the continuance of *Abstracts* in recent years was largely due to the generosity of the British chemical industry, which made it possible for the Chemical Society to make increased payments to the Bureau. The Society's contribution to the Bureau had been fixed by agreement at £5,300 per annum. In the four years 1950—53 the Chemical Society's payments have totalled £69,884. In 1952 the Councils of the Chemical Society and the Society of Chemical Industry decided with great reluctance that the two Societies could no longer carry the responsibility for the heavy expenditure of the Bureau and that the future annual payments of the two Societies must be limited to the sums guaranteed by agreement.

In this situation it clearly became necessary, if the publication of *Abstracts* was to continue, to make a new arrangement for financing the Bureau and for the continuance of publication.

Representations to H.M. Government were made through the Parliamentary and Scientific Committee, and at the request of the Lord President of the Council a committee was established by the Royal Society to enquire into the position. As a result of the recommendations of this committee a further appeal was issued to Industry in 1953, which raised £44,000. The Government also promised a contribution of £35,000. These payments made possible the continuance of *Abstracts* for 1953 and the publication of those Indexes that were in arrears. It was indicated, however, both by the Government and by Industry that contributions of this order would not be forthcoming in future. During the year, active attempts were made to arrange for the future publication of *Abstracts* on a commercial basis. Unfortunately, and after very exhaustive enquiries, this proved impracticable; so the Bureau will be dissolved on completion of its outstanding commitments.

Although *British Abstracts* have come to an end, purely for financial reasons, the Council recognises the need for an abstracting service that could be available to Fellows at a reasonable price. Every practical possibility is being investigated, and the Society has kept in touch with other bodies on this question. The Society was also represented, by an observer, at the meetings in Paris of the *ad hoc* committee on abstracting appointed by the International Union of Pure and Applied Chemistry.

5. *Current Chemical Papers.* The Council arranged for the publication, in 1954, of *Current Chemical Papers*, a classified world list of new papers in pure chemistry. This publication, whilst not replacing abstracts, will, it is hoped, give early information to chemists on work published in the world's literature.

6. *Journal Reprint Service.* The Council arranged that papers published in the *Journal* from January 1954 should be available from the Society in reprint form. Details have been circulated to all Fellows.

7. *List of Fellows.* A new edition of the *List of Fellows* (corrected to September 1952) was published during the year. Fellows may obtain copies from the General Secretary, price 2*s.* 6*d.*

IV. MEETINGS.

1. *Scientific Meetings.* Details of all meetings, including those held in London and those arranged at various centres by Local Representatives of the Society, are given in Appendix A.

2. *Anniversary Meetings.* The Anniversary Meetings were held in London on March 26th—27th.

3. *Centenary Lectures.* Professor A. Tiselius (Honorary Fellow) delivered a Centenary Lecture, entitled " Some Applications of the Separation of Large Molecules and Colloidal Particles," in London, Birmingham, and Glasgow.

V. LIBRARY.

The Report of the Joint Library Committee is given in Appendix B.

VI. OTHER ACTIVITIES.

1. *Grants for Research.* Grants from the Research Fund totalling £734 14*s.* 6*d.* were made to 30 applicants.

2. *Corday–Morgan Memorial Fund Executive.* The first report of the Executive appointed to administer, in accordance with the testator's wishes, grants made by the Society for the unification of the chemical profession within the British Empire is given in Appendix C.

3. *Corday–Morgan Medal and Prize.* The Corday–Morgan Medal and Prize for 1951 was awarded to Dr. Frederick Sanger.

4. *Royal Photographic Society.* Dr. W. H. Mills, on behalf of the Council, presented an Address at the Centenary Meeting of the Royal Photographic Society.

5. *Faraday Society.* A message of congratulation was conveyed to the Faraday Society on the occasion of its Jubilee Meeting on April 16th.

6. *Japanese Chemical Society.* Sir Robert Robinson, on behalf of the Council, presented an Address of congratulation at the Seventy-Fifth Anniversary Celebrations of the Japanese Chemical Society.

7. *Koninklijke Nederlandse Chemische Vereniging.* Professor H. Burton and the General Secretary represented the Society at the Fiftieth Anniversary Meetings of the Netherlands Chemical Society. An Address of congratulation was presented.

8. *Danish Chemical Society.* Dr. J. S. Anderson, Dr. J. Chatt, Dr. N. N. Greenwood, Dr. F. G. Mann, Dr. L. E. Orgel, Mr. H. M. Powell, and Dr. L. E. Sutton were delegates of the Society at a Symposium on Co-ordination Chemistry arranged by the Danish Chemical Society in Copenhagen on August 9th—14th.

9. *Gesellschaft Deutscher Chemiker.* Professor H. Burton, Professor E. D. Hughes, and the General Secretary attended the Annual Meetings of the German Chemical Society in Hamburg on September 14th—19th.

VII. ADMINISTRATION.

1. *Council.* At the Annual General Meeting on March 27th, the following were declared elected :

Vice-President who has not filled the Office of President	Professor R. D. Haworth.
Elected Ordinary Members of Council.....	Professor F. Bergel, Professor M. J. S. Dewar, Dr. I. J. Faulkner, Professor Brynmor Jones, Dr. A. I. Vogel.

2. *Local Representatives.* The following appointments have been made to fill vacancies among the Society's Local Representatives:

Birmingham	Dr. E. J. Bourne in place of Dr. L. L. Bircumshaw.
Cambridge	Dr. R. N. Haszeldine in place of Dr. B. Lythgoe.
Hull	Dr. W. B. Orr in place of Professor Brynmor Jones.
Liverpool	Dr. D. W. Broad in place of Mr. L. A. Haddock.
Northern Ireland	Dr. R. G. R. Bacon in place of Dr. H. Graham.
North Wales	Dr. J. E. McKail in place of Dr. W. Rogie Angus.
Nottingham	Dr. C. C. Addison in place of Dr. D. O. Jordan.
Sheffield	Mr. H. J. V. Tyrrell in place of Dr. A. H. Lamberton.
Southampton	Dr. N. B. Chapman in place of Dr. K. R. Webb.

VIII. FINANCE.

1. *Accounts.* The financial results for the year under review are much more satisfactory than could, with any confidence, have been forecast a year ago. In 1952, had it not been for grants received through the Chemical Council and the Royal Society, the Society's expenditure (excluding expenditure on *Abstracts*) would have exceeded its income by some £21,000. In 1953 the gap was bridged and, but for the need to make further large payments on account of *Abstracts*, no financial assistance from outside sources would have been required. Although this recovery in the Society's fortunes cannot yet be considered permanent, the improvement has amply justified the increase in the Fellowship subscriptions and in the prices charged to Fellows and to outside subscribers for the Society's publications. The following are notes on the more important items of Income and Expenditure.

(a) *Fellows' Subscriptions.* The increase in the basic annual subscription from £3 10*s.* to £4 10*s.*, introduced at the beginning of 1953, and the increased schedule price of certain publications have together increased the Society's income from its Fellows by over £9,000 in 1953. This is the largest single contribution made towards closing the gap between expenditure and income. Despite this very favourable result, however, the Council does not consider that a permanent solution has been found. Many Fellows, for a variety of reasons, require to receive only a very limited range of publications, or none at all. The Council has, therefore, proposed that, as from January 1955, the subscription rate shall be fixed at £2 2*s.*, and that publications, other than *Proceedings*, which will be free to all Fellows, shall be available for purchase at an extra charge by those Fellows that require them. Fellows under twenty-seven years of age, however, may continue to receive *Annual Reports* and *Quarterly Reviews* without payment. The right of existing Life Fellows to receive the *Journal*, or other publications of equivalent value, will be preserved. This new proposal is not expected to have any immediate effect on the Society's financial position, but it is hoped that the Society's Fellowship, and thus its income, will increase over a period of years through the retention of many of those Fellows who might otherwise have resigned.

(b) *Sale of Publications.* The income derived from the sale of publications to non-Fellows or to Libraries has increased by £8,865 as a result of the increase in the prices charged and a slight increase in circulation.

(c) *Grants Received to Assist Publication.* A grant of £3,500 was received through the Royal Society from the Government Scientific Grant-in-Aid for Scientific Publications, and the Council acknowledges this substantial assistance with gratitude. In addition, the Society has benefited to the extent of £16,600 by Grants received from the Chemical Council. These were made possible by the response of Industry to the Appeal issued by the Chemical Council for funds to help meet the cost of publication of original research work and the Council records its thanks to the Chemical Council and to Industry for this valuable and generous help.

These contributions have enabled the Society to continue the prompt publication of all suitable papers received. Without them, serious restrictions would have been necessary in view of the heavy commitments of the Society in respect of *Abstracts*.

(d) *Administrative Costs.* At £7,619 these are £440 higher than in 1952, but the total is not unreasonable when compared with the average cost for the preceding five years (£7525).

(e) *Cost of the* Journal. The Society's expenditure on the *Journal* was some £8,896 lower than in 1952. This results from the decreased size (4200 text pages compared with 5056 in 1952). The basic costs, with the exception of paper, which was reduced in price, have again risen slightly during the year. Moreover, it seems probable that the reduction in total expenditure is only temporary, since the number of communications suitable for publication received during the last three months of 1953 has increased.

(f) *Abstracts.* The Society's contribution to the Bureau of Abstracts totalled £17,800. This relates largely to expenditure to be incurred in the completion of outstanding indexes not fully provided for in previous years.

An account of the events leading up to closing of the Bureau of Abstracts is given in Section III of this Report.

Comparable figures for the major items in the accounts, detailed above, are given in Table 6.

TABLE 6.

	Income.			*Expenditure.*		
	Annual subscriptions (net).	Sale of publications.	Outside grants.	Administration.	Journal of the Society.	Contributions to Bureau of Abstracts.
	£	£	£	£	£	£
1948	20,754	9,503	3,400	7,855	19,997	5,300
1949	22,629	13,778	5,233	7,492	31,963	5,300
1950	26,884	16,784	15,984	7,468	31,713	12,084
1951	26,928	22,358	33,500 *	7,632	36,309	14,000
1952	29,273	21,365	49,550	7,178	53,439	26,000
1953	38,801	30,231	20,100	7,619	44,542	17,800

* Includes £9500 in respect of previous years.

2. *Subscriptions under Deed of Covenant.* The Society has continued to benefit from the Income Tax recovered on the annual subscriptions of those Fellows who have entered into Deeds of Covenant with the Society in respect of their annual subscriptions. A total of £3597 has been recovered during the last three years.

3. *Library.* The Council records its thanks for a grant of £712 from the Chemical Council towards maintenance costs of the Library and to those Societies that, in return for the use of the Library by their members, have continued to contribute towards maintenance costs. The Chemical Society's contribution towards Library expenses was £3,402, of which £2,490 was for expenditure of a capital nature.

4. *Investments.* In the past it has been customary for the Society to invest available funds in Trustee Securities. During the year, after taking Counsel's opinion, it was confirmed that investments on the General Purposes Account or Special Reserve Fund need not be confined to these stocks. The Council accordingly considered it advisable that part of the Society's funds should be invested outside the very limited range of Trustee Securities and, following consultations with the Society's brokers, and on the recommendation of the Finance and General Purposes Committee, some £10,000 was re-invested in non-Trustee Securities. This resulted in an increase in investment income in 1953, and a further small improvement can be expected in the future when the new dividends are received over a full year.

In addition, Centenary Fund Investments have been increased by the purchase of £2667 19*s.* 5*d.* 4% Consolidated Stock at a cost of £2500. £100 3% Defence Bonds (3rd issue) held on Special Reserve Fund has been converted into 3½% Defence Bonds, and £150 2½% National War Bonds, 1951/53, on Staff Pensions Fund, has been repaid at par.

IX. REPRESENTATIVES OF THE SOCIETY ON OTHER BODIES.

In 1953 the Society was represented on various bodies by the following :

" Acta Metallurgica " :

International Journal of the Science of Metals : Dr. U. R. Evans.

Association of British Chemical Manufacturers :

Joint Technical Committee on Patents : Dr. J. T. Hewitt.

Barker Committee :

Formed to support the publication of the Barker Index of the characteristic angles of crystalline compounds : Dr. G. M. Bennett.

Bristol University Court :

Professor C. E. H. Bawn.

British National Committee for Chemistry :

Sir Eric Rideal, Professor E. D. Hughes, Professor M. Stacey.

British National Committee for Crystallography :

Professor J. M. Robertson.

British Standards Institution. Technical Committees :

C/17.	Viscosity : Dr. A. E. Dunstan.
C/34.	Standardisation of pH Scale : Professor H. T. S. Britton.
CHE/36.	Chemicals for Electroplating : Dr. J. R. I. Hepburn.
DAC/-.	Standards for Dairying Chemistry : Mr. Eric Voelker.
FCC/HCC/1.	Nomenclature for Fine and Heavy Chemicals Industries : The Editor.
HCC/2.	Silica Gel : Dr. B. Lambert.
LBC/-.	Scientific Glassware and Related Laboratory Apparatus : Dr. G. R. Davies.
LBC/1/1.	Dean and Stark and Ubbelohde Apparatus : Dr. G. R. Davies.
LBC/5.	Hydrometers : Mr. R. Sutcliffe.
LBC/6.	Standard Distillation Apparatus : Mr. R. Sutcliffe.
LBC/11.	Microchemical Apparatus : Mr. R. Belcher, Dr. H. D. K. Drew.
LBC/11/1.	Apparatus for Microchemical Combustion Methods : Dr. R. Belcher.
LBC/11/3.	Accessory Apparatus connected with Gravimetric Microanalysis : Mr. R. Belcher.
LBC/16.	Standardization of Glass Electrodes : Dr. D. J. G. Ives.
LBC/17.	Apparatus Drawing Conventions : The Editor.
LBC/18.	Laboratory Furniture and Fittings : Mr. R. Sutcliffe.
PAC/13.	Laboratory Filter Papers : Mr. F. H. Burstall.
PCC/1.	Nomenclature for Insecticides : Professor R. L. Wain.
RUC/8.	Rubber Tubing and Bungs for Laboratory Use : Dr. L. C. Bateman.
USM/1.	Units and Technical Data : The Editor.
USM/1/7.	Standard Glossary of Nuclear Terms : The Editor.
USM/2.	Units, Symbols, and Abbreviations : The Editor.

Bureau of Abstracts. Continuing Committee :

Sir Wallace Akers, Dr. G. M. Bennett, Dr. G. M. Dyson, Professor H. Burton.

Chemical Council :

The Treasurer, Mr. R. P. Bell, Professor C. K. Ingold, Professor E. D. Hughes.

City and Guilds of London Institute :

The President.

Faraday Society. Colloidal and Biophysics Committee :

Dr. P. Johnson.

Joint Library Committee :

Dr. L. C. Bateman, Dr. J. H. Burgoyne, Professor M. J. S. Dewar, Dr. F. Fairbrother, Dr. J. E. Garside, Dr. J. Kenyon, Professor K. Lonsdale, Dr. A. Maccoll, Professor H. N. Rydon, Dr. L. E. Sutton, Professor C. Tyler, Professor R. L. Wain, Dr. J. Walker, Professor W. Wardlaw.

Lawes Agricultural Trust. Committee of Management :

Sir John Simonsen.

Parliamentary and Scientific Committee :

The President, The General Secretary.

Regional Council for Further Education for the South-West. Chemistry and Chemical Technology Committee :

Professor W. E. Garner.

Royal Society. Joint Standing Committee for Symbols and Abbreviations :

Mr. R. P. Bell, The Editor.

Royal Society. Scientific Societies Accommodation Committee :

The President.

Society of Dyers and Colourists. Perkin Centenary Committee :

Dr. M. A. T. Rogers.

Yorkshire Council for Further Education. Advisory Committee for Chemistry in South and East Yorkshire :

Professor R. D. Haworth.

APPENDIX A.

MEETINGS HELD DURING 1953.

IN LONDON.

(Meetings were held in the Rooms of the Society at Burlington House unless otherwise stated.)

January 22nd, *Pedler Lecture*, "Discoveries among Conjugated Macrocyclic Compounds," by Professor R. P. Linstead; February 5th, *Symposium*, "Acetylene Chemistry," arranged by Professor E. R. H. Jones (contributions from the following were read and discussed—Dr. E. A. Braude, Dr. M. C. Whiting, Dr. R. N. Lacey, Mr. H. W. B. Reed, Dr. B. C. L. Weedon, Dr. R. A. Raphael, Professor E. R. H. Jones, Professor N. A. Sörensen, Dr. W. D. Celmer and Dr. I. A. Solomons, and Dr. B. Lythgoe); March 19th, *Nernst Memorial Lecture*, by Professor J. R. Partington; April 30th, *Lecture*, "The Scientific Problems of Surface Catalysis," by Professor H. S. Taylor; May 7th, *Meeting* for the reading of original papers; June 4th, *Meeting* to commemorate the present-day aspects of the work of Sir William Ramsay (President, 1907–9) (contributions from the following were read and discussed—Dr. J. S. Anderson, Professor F. A. Paneth, Dr. H. G. Jenkins, Dr. L. C. Bannister, Mr. H. J. Taylor); October 15th, at the Royal Institution, *Tilden Lecture*, "The Mechanisms of Reactions between Gases and Solids," by Dr. J. S. Anderson; November 5th, at the Imperial College of Science and Technology, *Tilden Lecture*,

" Aromatic Character in Seven-membered Ring Systems," by Dr. A. W. Johnson; November 19th, at the Institution of Civil Engineers, *Centenary Lecture*, " Some Applications of the Separation of Large Molecules and Colloidal Particles," by Professor A. Tiselius; December 3rd, *Meeting* for the reading of original papers; December 17th, *Meeting* for the reading of original papers.

OUTSIDE LONDON.

Aberdeen. At Robert Gordon's Technical College unless otherwise stated: February 11th, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, *Lecture*, " Selective Herbicides and the Principles of Selective Toxicity," by Professor G. E. Blackman; at the University, Old Aberdeen, March 12th, *Official Meeting and Pedler Lecture*, " Discoveries among Conjugated Macrocyclic Compounds," by Professor R. P. Linstead; joint meetings with the Royal Institute of Chemistry and the Society of Chemical Industry: March 26th, *Lecture*, " Some Recent Developments in the Field of Lipids," by Dr. J. A. Lovern; October 23rd, *Lecture*, " Structure, Stereochemistry, and Inclusion Compounds of Some Phenol Derivatives," by Professor W. Baker; November 20th, *Lecture*, " The Production, Fabrication and Properties of Titanium," by Dr. N. P. Inglis; at the University, December 17th, *Lecture*, " Some Aspects of Chemical Engineering," by Mr. H. W. Cremer.

Birmingham. Joint meetings with the University Chemical Society, at the University: January 23rd, *Lecture*, " Usnic Acid and its Derivatives," by Professor A. Robertson; March 13th, *Lecture*, " Changes occurring in the Surface of Solids during Chemical Reactions," by Professor W. E. Garner; October 23rd, *Lecture*, "Analytical Errors: Heinous and otherwise," by Dr. T. B. Smith; November 20th, *Centenary Lecture*, " Some Applications of the Separation of Large Molecules and Colloidal Particles," by Professor A. Tiselius; December 4th, *Lecture*, " Some Intermolecular Compounds," by Mr. H. M. Powell.

Bristol. Joint meetings with the Royal Institute of Chemistry and the Society of Chemical Industry, held at the University unless otherwise stated: January 22nd, at Gloucester Technical College, *Lecture*, " Biogenesis of Caratenoids," by Dr. T. W. Goodwin; January 29th, *Lecture*, " Progress in Hydrogen-bond Chemistry," by Professor L. Hunter; February 5th, at Gloucester Technical College, *Lecture*, " The Practical Approach to Chemotherapy," by Dr. F. L. Rose; February 25th, with the Plastics Institute, *Lecture*, " Construction of the British Resin Factory at Barry," by Mr. T. W. M. Ponds; March 19th, *Lecture*, " Some New Applications of Infra-red Spectroscopy," by Dr. H. W Thompson; May 5th, with the Institute of Fuel, *Lecture*, " Research and Development on Refractory Materials," by Dr. A. T. Green; October 1st, *Lecture*, " The Changing Pattern of Plant Design in the Basic Chemical Industries," by Mr. Stanley Robson; October 15th, *Lecture*, " Synthesis of Simple Peptides," by Professor F. E. King; November 5th, *Lecture*, " Some Aspects of the Work at Rothamsted," by Sir William Ogg; November 19th, at the Grand Hotel, Social Evening and Film Show; November 19th, *Lecture*, " Mechanism of Detergent Action," by Professor N. K. Adam; November 26th, at Gloucester Technical College, *Lecture*, " Some Advances in the Chemistry of Organic Fluorine Compounds," by Professor M. Stacey; December 3rd, with the Institute of Metals, *Lecture*, " Metallurgical Trends of Interest to the Chemical Industry," by Mr. L. Rotherham.

Cambridge. October 30th, joint meeting with the University Chemical Society, *Lecture*, " The Polymerisation of Sulphur," by Professor G. Gee, at the Chemical Laboratory, Pembroke Street.

Edinburgh. Joint meetings with the Royal Institute of Chemistry and the Society of Chemical Industry: January 15th, at the Heriot-Watt College, *Lecture*, " Vitamin B_{12} and Related Factors," by Dr. E. Lester Smith; February 3rd, at the Biochemistry Lecture Theatre, Teviot Place, *Lecture*, " Bacterial Polysaccharides," by Professor M. Stacey; at the North British Station Hotel: February 19th, *Lecture*, " The Fertiliser, Phosphorus and Allied Industries," by Dr. B. Raistrick; March 19th, *Lecture*, " Radiation Chemistry," by Professor F. S. Dainton; October 15th, *Lecture*, " River Pollution," by Dr. E. A. B. Birse;

November 12th, *Lecture*, "The Mechanism of Hydrochloric Production Acid in the Stomach," by Dr. R. E. Davies; December 10th, *Lecture*, "Chemotherapy and the Organic Chemist," by Dr. F. L. Rose.

Exeter. At the Washington Singer Laboratories: February 27th, *Lecture*, "Physical Chemistry of Acetaldehyde and Some of its Reactions," by Mr. R. P. Bell; November 19th, *Lecture*, "The Synthesis of Nucleotide Co-enzymes," by Professor A. R. Todd.

Glasgow. January 16th, at the Royal Technical College, *Meeting* for the reading of original papers; February 20th, at the University, Annual General Meeting of Local Fellows followed by a *Lecture*, "Allene Chemistry," by Professor E. R. H. Jones; March 13th, at the Marlborough, Ramsay Chemical Dinner; October 23rd, joint meeting with the Andersonian Chemical Society and the Alchemists' Club, at the Royal Technical College, *Lecture*, "Fluorescence of Solutions," by Dr. E. J. Bowen; November 20th, at the University, *Lecture*, "Some Intermolecular Compounds," by Mr. H. M. Powell; November 25th, at the University, *Centenary Lecture*, "Some Applications of the Separation of Large Molecules and Colloidal Particles," by Professor A. Tiselius.

Hull. Joint meetings with the University College Scientific Society, at University College: January 29th, *Lecture*, "The Third Dimension in Chemistry," by Dr. A. F. Wells; November 26th, *Lecture*, "Aromatic Substitution," by Professor M. J. S. Dewar.

Irish Republic. January 14th, joint meeting with the Institute of Chemistry of Ireland, at University College, Dublin, *Lecture*, "The Use of Lithium Aluminium Hydride in Organic Chemistry," by Dr. Dermot Twomey; at Trinity College, Dublin, unless otherwise stated: February 25th, joint meeting with the Institute of Chemistry of Ireland, *Lecture*, "Some Aspects of the Chemistry of Butenolides," by Professor Wesley Cocker; March 13th, joint meeting with the Werner Society, *Lecture*, "Crystal and Molecular Structure—*X*-Ray and Electron-microscope Studies," by Professor J. M. Robertson. Joint meetings with the Royal Institute of Chemistry, the Society of Chemical Industry, and the Institute of Chemistry of Ireland, April 15th, at University College, Dublin, April 16th, at Cork, and April 18th, at University College, Galway, *Lecture*, "The Influence of Chemistry on Medical Practice," by Professor E. C. Dodds; May 29th, joint meeting with the Werner Society, *Lecture*, "The Behaviour of Hydrogen Peroxide as a Solvent," by Professor W. F. K. Wynne-Jones; October 21st, at University College, Dublin, *Lecture*, "Phosphates in Biochemical Reactions," by Dr. A. K. Mills; November 20th, joint meeting with the Werner Society, *Lecture*, "Recent Work in Terpene Chemistry," by Sir John Simonsen.

Leeds. At the University: January 19th, *Royal Institute of Chemistry Lecture*, "Some Peculiar Properties of Mineral Dusts," by Professor H. V. A. Briscoe; February 16th, *Royal Institute of Chemistry Lecture*, "Chromatography in the Study of Amino-acid Metabolism," by Dr. C. E. Dent; March 3rd, joint meeting with the University Chemical Society, *Lecture*, "The Non-Steady State in Chemical Kinetics," by Professor H. W. Melville; November 3rd, *Lecture*, "Pernitrous Acid and its Nitrating and Hydroxylating Properties," by Mr. R. Heslop; November 23rd, *Royal Institute of Chemistry Lecture*, "Some Experiences of Food Legislation during War," by Sir Harry Jephcott. Fellows were invited to all meetings of the Royal Institute of Chemistry, Leeds Area Section, as well as to those organised by other bodies.

Liverpool. At the University, joint meetings with the Royal Institute of Chemistry, Society of Chemical Industry, British Association of Chemists, and the University Chemical Society: January 22nd, *Lecture*, "Chemical Aspects of Drug Metabolism," by Professor R. T. Williams; February 26th, *Lecture*, "Recent Studies relating to Hydrocarbon Oxidation," by Professor A. R. Ubbelohde; October 22nd, *Lecture*, "Reaction Mechanism and Molecular Geometry," by Professor C. W. Shoppee; November 19th, *Tilden Lecture*, "The Mechanisms of Reactions between Gases and Solids," by Dr. J. S. Anderson.

Manchester. At the University, unless otherwise stated: January 27th, *Meeting* for the reading of original papers; February 3rd, *Official Meeting and Tilden Lecture*, "The Chemistry of Intermolecular Compounds," by Mr. H. M. Powell; March 27th, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, *Symposium* "Corrosion Inhibitors"; April 10th, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, at the College of Technology, *Lecture*, "Nature of

Toxic Action," by Dr. M. W. Goldblatt; October 22nd, at the College of Technology, *Meeting* for the reading of original papers; November 19th, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, *Lecture*, " Manufacture of Chemicals from Petroleum," by Dr. J. L. Edgar; December 4th, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, *Lecture*, " Chemistry and Pharmacological Reactions," by Mr. J. W. Trevan.

Newcastle and Durham. At King's College, Newcastle-on-Tyne, unless otherwise stated: February 13th, *Bedson Club Lecture*, " The Molecular-orbital Theory of Organic Chemistry," by Professor M. J. S. Dewar; February 27th, *Meeting* for the reading of original papers; March 13th, *Bedson Club Lecture*, " Catalytic Inorganic Halides and the Friedel–Crafts Reaction," by Dr. F. Fairbrother; May 8th, *Bedson Club Lecture*, " Allene Chemistry," by Professor E. R. H. Jones; October 23rd, *Meeting* for the reading of original papers; November 13th, *Bedson Club Lecture*, " The Third Dimension in Chemistry," by Dr. A. F. Wells; November 19th, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, at the Science Buildings, Durham, *Lecture*, " Some Intermolecular Compounds," by Mr. H. M. Powell; November 27th, *Bedson Club Lecture*, " Contributions of Optical Activity to the Study of Some Chemical Reactions," by Dr. J. Kenyon. Fellows were invited to the meetings of the Bedson Club.

Northern Ireland. At Queen's University, Belfast, joint meetings with the Royal Institute of Chemistry and the Society of Chemical Industry: February 16th, *Lecture*, " The Work of the British Coal Utilisation Research Association," by Dr. D. T. A. Townend; March 6th, with the Andrews Club, *Lecture*, " The Scientific Examination of Paintings," by Dr. A. E. Werner; May 19th and 20th, Symposium on Eggs; October 13th, *Lecture*, " Tin, Tinplate, and Tin Coatings," by Mr. W. E. Hoare; October 29th, *Lecture*, " The Comparative Chemistry of Carbon and Silicon," by Professor E. D. Hughes.

North Wales. January 29th, joint meeting with the University College Chemical Society at the Edward Davies Chemical Laboratories, Aberystwyth, *Lecture*, " Reaction Mechanism and Molecular Geometry," by Professor C. W. Shoppee; at University College of North Wales, Bangor: February 12th, joint meeting with the Liverpool Section of the Society of Chemical Industry and the University College of North Wales Chemical Society, *Lecture*, " The Protein Requirements of the Ruminant Animal," by Dr. R. L. M. Synge; March 12th, joint meeting with the Chemical Societies of the University of Liverpool and University College of North Wales, *Lecture*, " The Deoxy-sugars and their Significance as Constituents of Natural Products," by Professor M. Stacey; April 30th, joint meeting with the University College of North Wales Chemical Society, *Lecture*, " Some Properties of High-polymer Solutions," by Professor C. E. H. Bawn; November 19th, joint meeting with the University College of North Wales Chemical Society, *Lecture*, " Electron-transfer Reactions," by Professor F. S. Dainton.

Nottingham. Joint meetings with the University Chemical Society, at the University, unless otherwise stated: January 19th, joint meeting with the Leicester University College Chemical Society, at University College, Leicester, *Lecture*, " Resonance," by Professor C. A. Coulson; January 29th, *Lecture*, " Experiments with Radioactive and Stable Isotopes," by Professor F. S. Dainton; February 19th, *Lecture*, " Certain Aspects of the Chemistry of Sesquiterpenes," by Professor G. R. Clemo; March 3rd, joint meeting with Leicester University College Chemical Society, at University College, Leicester, *Lecture*, " Molecular Vibrations and Chemical Problems," by Dr. H. W. Thompson; October 29th, *Lecture*, " Allene Chemistry," by Professor E. R. H. Jones; November 2nd, joint meeting with Leicester University College Chemical Society, at University College, Leicester, *Lecture*, " Some Problems raised by the Visualisation of Big Molecules," by Dr. R. W. G. Wyckoff; November 26th, *Official Meeting and Tilden Lecture*, " Aromatic Character in Seven-membered Ring Systems," by Dr. A. W. Johnson; November 30th, joint meeting with Leicester University College Chemical Society, at University College, Leicester, *Lecture*, " The Structures of Some Electron-deficient Solids," by Professor H. C. Longuet-Higgins.

St. Andrews and Dundee. January 8th, at University College, Dundee, *Lecture*, " Some Aspects of Sorption," by Professor R. M. Barrer; January 23rd, joint meeting with St.

Andrews University Chemical Society, at United College, St. Andrews, *Lecture*, "Chromatography," by Dr. R. L. M. Synge; January 30th, at United College, St. Andrews, *Official Meeting and Lecture*, "The Study of Combustion by the Method of Flash Photolysis," by Professor R. G. W. Norrish; February 13th, at United College, St. Andrews, *Lecture*, "Colouring Matters of Dragon's Blood Resin and Related Topics," by Professor A. Robertson; February 20th, at University College, Dundee, *Royal Institute of Chemistry Lecture*, "The Significance of Kékulé Structures for the Stability of Aromatic Hydrocarbons," by Dr. Eric Clar; March 2nd, at University College, Dundee, *Lecture*, "Light Scattering," by Dr. E. J. Bowen; March 20th, at University College, Dundee, *Royal Institute of Chemistry Lecture*, "The Production and Refining of Shale Oil," by Dr. G. H. Smith; April 9th, at University College, Dundee, *Lecture*, "Some Equilibria and Reactions with Sulphur," by Dr. G. Gee; April 24th, joint meeting with the University Chemical Society, at United College, St. Andrews, *Lecture*, "Metal Halide Catalysts," by Dr. F. Fairbrother; May 8th, at United College, St. Andrews, *Royal Institute of Chemistry Lecture*, "Some Developments in the Chemistry of Cortisone," by Professor F. S. Spring; October 16th, joint meeting with the University Chemical Society, at United College, St. Andrews, *Lecture*, "Chemistry at St. Andrews: a Historical Survey," by Professor J. Read; October 22nd, at University College, Dundee, *Lecture*, "Structure, Stereochemistry, and Inclusion Compounds of Some Phenol Derivatives," by Professor W. Baker; November 13th, joint meeting with the University Chemical Society, at United College, St. Andrews, *Lecture*, "The Stereochemistry of *cyclo*Hexane Derivatives," by Professor D. H. R. Barton.

Sheffield. Joint meetings with the University Chemical Society, at the University: February 5th, *Lecture*, "Nascent Hydrogen: a Re-interpretation," by Professor F. S. Dainton; February 26th, *Lecture*, "Electrode Kinetics," by Dr. J. O'M. Bockris; March 12th, *Lecture*, "The Biogenesis of Plant Products," by Sir Robert Robinson; October 29th, *Lecture*, "Structure, Stereochemistry, and Inclusion Compounds of some Phenol Derivatives," by Professor W. Baker; November 26th, with the Royal Institute of Chemistry, *Lecture*, "Infra-red Spectroscopy and Chemical Problems," by Dr. H. W. Thompson.

Southampton. At the University, joint meetings with the University Chemical Society, unless otherwise stated: January 23rd, with the Royal Institute of Chemistry, *Lecture*, "Chemical Reactions induced by Nuclear Radiations," by Professor F. S. Dainton; February 13th, *Lecture*, "The Synthesis of Sugars," by Dr. J. K. N. Jones; March 13th, with the Royal Institute of Chemistry, *Lecture*, "The Mechanism of Detergent Action," by Professor N. K. Adam; October 13th, joint meeting with the Portsmouth and District Chemical Society, at the Municipal College, Portsmouth, *Lecture*, "The Manufacture of Sulphuric Acid from Anhydrite," by Dr. J. S. Dunn; November 6th, with the Royal Institute of Chemisty, *Lecture*, "The Bacteriostatic Properties of Heterocyclic Compounds," by Professor A. Albert; November 27th, *Lecture*, "Anionotropy," by Dr. E. A. Braude.

South Wales. February 6th, joint meeting with University College of Swansea Chemical Society, at University College, Swansea, *Lecture*, "Some Recent Developments in the Investigation of Radical Reactions," by Professor H. W. Melville; March 13th, joint meeting with the University College Chemical Society and the Royal Institute of Chemistry, at University College, Swansea, *Lecture*, "Acids containing Fluorine," by Professor M. Stacey; May 14th, joint meeting with the University College of Swansea Chemical Society, at University College, Swansea, *Lecture*, "Structural Relations of Natural Products," by Sir Robert Robinson; October 26th, at University College, Cardiff, *Lecture*, "Methods of Measuring Reaction Velocities in Solution," by Mr. R. P. Bell; November 20th, joint meeting with the University College of Swansea Chemical Society and the Royal Institute of Chemistry, at University College, Swansea, *Lecture*, "The Scope and Application of *X*-Ray Methods in Organic Chemistry," by Professor J. M. Robertson; November 27th, at University College, Swansea, *Tilden Lecture*, "The Mechanisms of Reactions Between Gases and Solids," by Dr. J. S. Anderson.

APPENDIX B.

ANNUAL REPORT OF THE JOINT LIBRARY COMMITTEE FOR THE YEAR 1953.

Library facilities continue to be used to capacity. The attendances by readers in the year showed a slight decrease, numbering 10,140 against 10,562 in the previous year. Books borrowed were 399 less than in 1952, and the number of pages of which photocopies were made, 2,639, showed a decrease of 1,068. During the year a Remflex Copier was installed, and 1,572 of the pages mentioned were copied by this means. The figures quoted do not include the copying of infra-red spectrograms which are sold by the Society. Telephone enquiries increased by 184, and reached a total of 2,552. There was a gratifying increase in the number of books presented. No less than 99 of a total of 362 books added were donations. The Committee warmly appreciates the courtesy of Authors, Publishers, and others who have added to the value of the Library by such gifts. The total number of volumes in the Library is now 54,915, of which 16,893 are books and 38,122 are complete volumes of periodicals. The following figures indicate the growth of the Library and the use made of it :

			Additions.		
	Attendances.	Books borrowed.	Books added.	Volumes of periodicals.	Pamphlets.
1953	10,140	8,304 (3,326 by post)	362	815	143
1952	10,562	8,703 (3,526 by post)	378	716	202
1951	10,489	9,091 (3,795 by post)	358	712	366
1950	10,415	8,294 (3,284 by post)	422	899	233

The bequest of the Ogilvie collection of books on the production and refining of sugar and the cultivation of sugar cane, although a most welcome addition to the Library, has served to stress the acute need for adequate accommodation for the Library. It is clear that the possibilities of the present building have been exhausted. The only alternative is to secure accommodation elsewhere, within easy reach of Burlington House, to allow for a minimum of ten years' growth. This matter is now receiving urgent consideration.

APPENDIX C.

FIRST REPORT OF THE CORDAY-MORGAN MEMORIAL FUND EXECUTIVE.

Sir Gilbert Morgan, who died on February 1st, 1940, made a bequest to the Chemical Society, subject to a life interest to his widow, to be used, in part, for the establishment of a capital fund to be known as the Corday–Morgan Memorial Fund. The Testator decreed that the income arising from this fund should be applied by the Chemical Society to assist in the unification of the chemical profession within the British Empire by grants or other awards to some representative body of British Chemists.

The Council of the Chemical Society felt that the wishes of its benefactor could best be met by the appointment of an Executive on which the Chemical Society, the Royal Institute of Chemistry, and the Society of Chemical Industry (the "Three Chartered Chemical Bodies") were represented and, with the agreement of the various councils, the Corday–Morgan Memorial Fund Executive, consisting of the Presidents and immediate Past-Presidents of the Three Chartered Bodies, was formed.

In accordance with the bequest, the Council of the Chemical Society made grants of £400 to the Executive in each of the years 1951 and 1952. The Executive in its turn has decided to appoint each year, if sufficient funds are available, a Corday–Morgan Commonwealth Fellow who shall be a graduate from a Commonwealth country specified each year by the Executive. The Executive is empowered to administer grants received from other sources. The Fellowship is intended to provide an opportunity for post-doctorate (or

equivalent) study, and it is tenable at a University in any part of the Commonwealth outside the home country of the Fellow appointed. The Executive believes that in this way it can best meet the wishes of the late Sir Gilbert Morgan and can assist in promoting the free interchange of chemical knowledge and ideas between the various countries of the Commonwealth.

The first award of a Corday–Morgan Commonwealth Fellowship was made, in October 1952, to Dr. H. J. Anderson, a graduate from the University of Manitoba who had subsequently held a research fellowship at the North-western University. Dr. Anderson now holds his Corday–Morgan Commonwealth Fellowship for one year at The Dyson Perrins Laboratory, Oxford. The award for 1953 has been made to Dr. A. D. Campbell, a graduate of the University of Otago, New Zealand, who will undertake research at the University of Glasgow. The Executive has agreed that the next Fellowship to be awarded should be offered to an Australian graduate.

The constitution of the Executive and the accounts for the period ending December 31st, 1952, are reproduced below.

CONSTITUTION.

1. The Executive shall consist of the Presidents and immediate Past Presidents of respectively the Chemical Society, the Royal Institute of Chemistry, and the Society of Chemical Industry (hereafter referred to as the " Three Chartered Bodies "), provided always that if the President or immediate Past President of any of the Three Chartered Bodies shall inform the Council of that body that he is unable to serve as a member of the Executive, the Council of that body shall be at liberty to appoint some other person in his place either generally or for such period as may be specified, and during the currency of such appointment the person so appointed shall for all purposes be a member of the Executive in place of the President or Past President in whose stead he was appointed.

2. The purpose of the Executive shall be :

(i) To advise the Councils of the Three Chartered Bodies upon any matter affecting the interests of the Three Chartered Bodies which may have been referred to the Executive or which the Executive may wish to bring to the notice of one or more of the Three Chartered Bodies.

(ii) To administer such grants as may from time to time be made to it by the Council of the Chemical Society from the Corday–Morgan Memorial Fund for the purpose of assisting in the unification of the chemical profession within the Commonwealth and Empire, and to report to the Council of the Chemical Society concerning the expenditure of such grants.

(iii) To administer such other monetary grants as may from time to time be made to the Executive for the purpose of the general advancement of the science of chemistry within the Commonwealth and Empire.

3. The Executive shall appoint a Secretary who, subject to the Council of the Chemical Society raising no objection, shall be the General Secretary of the Chemical Society.

4. The Secretary shall summon such meetings as he may, from time to time, be directed to summon by the Executive, or upon receiving a request in writing from any two members of the Executive shall summon a special meeting. Not less than two weeks' notice shall be given of any such special meeting.

5. Four members of the Executive shall constitute a quorum at all meetings.

6. A banking account shall be opened in the name of the Executive, and no payments shall be made from this account unless the same be authorised by the Executive.

7. The Executive shall submit to the Councils of the Three Chartered Bodies each year, a Report of its activities for the past year, together with an audited Statement of its Accounts.

8. The expenses of the Executive shall be defrayed out of such grants as may be made to the Executive for the purpose of meeting its expenses by the Three Chartered Bodies.

CORDAY-MORGAN MEMORIAL FUND EXECUTIVE.

INCOME AND EXPENDITURE ACCOUNT FOR THE PERIOD NOVEMBER 17TH, 1951, TO DECEMBER 31ST, 1952.

Expenditure.	£	s.	d.	*Income.*	£	s.	d.
To Fellowship Grant	700	0	0	By Grants from the Corday-Morgan Memorial Fund for the years 1951/52	800	0	0
,, Miscellaneous Expenses		8	0	,, Interest on Deposit	6	9	8
,, Balance being excess of Income over Expenditure ...	106	1	8				
	£806	9	8		£806	9	8

C. K. INGOLD,
Chairman of the Executive.

J. R. RUCK KEENE,
Secretary of the Executive.

We have examined the above Income and Expenditure Account with the Books and Vouchers of the Executive, and certify them to be in accordance therewith and, in our opinion, correct. We have also verified the Balance at the Bankers.

FINSBURY CIRCUS HOUSE,
BLOMFIELD STREET, E.C.2.
March 11th, 1953.

W. B. KEEN AND CO.,
Chartered Accountants.

THE CHEMICAL SOCIETY

INCOME AND EXPENDITURE ACCOUNTS for the Year ended 31st December, 1953.

GENERAL PURPOSES.

1952			*Income.*	1953				1952				*Expenditure.*	1953			
£	s.	d.		£	s.	d.	£ s. d.	£	s.	d.	£ s. d.		£	s.	d.	£ s. d.
14,756	4	11	Separate Subscriptions—									Administration Expenses:				
242	7	7	On account of 1953	20,539	18	0		4,811	9	7		Salaries, Wages, Superannuation, etc.	5,231	1	7	
			On account of 1952 and previous years	269	5	5		697	4	0		House Expenses, etc.	617	18	11	
12,776	14	10	Joint Subscriptions—					813	13	8		Office Expenses and Stationery ...	579	0	6	
88	10	1	On account of 1953	16,648	17	1		270	18	3		Postages	284	19	9	
			On account of 1952 and previous years	49	16	9		—	—	—		Furniture	347	18	2	
27,863	17	5		37,507	17	3		585	3	10		Miscellaneous	557	13	7	
1,409	1	11	*Add* Income Tax recovered on Subscriptions under Covenant	1,292	18	0					7,178 9 4					7,618 12 6
											1,305 5 1	Expenses of Conjoint Chemical Office ...				1,329 3 8
											36 15 0	Subscriptions				36 15 0
											712 12 6	Expenses of Meetings				988 3 10
											480 4 1	Expenses of Local Representatives ...				526 0 9
											585 7 2	Travelling Expenses				518 13 4
												Transfers to:				
								13,656	2	10		Publications Account	18,081	16	2	
												Library Account:				
								2,453	1	8		Capital Expenditure	2,490	0	1	
								842	0	5		Maintenance	912	10	10	
												Special Reserve Fund:				
								—	—	—		Publications Reserve	3,000	0	0	
								—	—	—		Building and Equipment Reserve ...	1,000	0	0	
								—	—	—		Investments Reserve	1,500	0	0	
								800	0	0		Staff Pensions Fund	2,000	0	0	
											17,751 4 11					28,984 7 1
											2,513 11 8	Balance, being Excess of Income over Expenditure, carried to Balance Sheet				291 16 2
											£30,563 9 9					£40,293 12 4
							£40,293 12 4									
							£30,563 9 9									

Income and Expenditure Accounts for the Year ended 31st December, 1953.

PUBLICATIONS.

1952			*Income.*	1953				
£	s.	d.		£	s.	d.	£	s. d.
			Publication Sales (including back numbers):					
14,705	19	11	Journal and Proceedings	23,517	17	5		
2,162	16	0	Annual Reports on Progress of Chemistry	2,383	13	5		
2,018	16	10	Quarterly Reviews	1,919	9	3		
2,286	10	3	Authors' Extra Reprints	2,139	16	5		
			Abstracts (Back numbers only 1944 and earlier)	96	9	5		
163	10	10	Other Publications	173	5	1		
27	9	5						
							30,230	11 0
		21,365	3 3					
			Proceeds of Advertisements:					
1,193	3	1	Journal	1,172	10	9		
187	18	0	Annual Reports	182	4	5		
59	19	3	Quarterly Reviews	36	12	4		
							1,391	7 6
		1,441	0 4					
		367	14 0	Dividends on Investments			367	14 0
			Grants:					
5,800	0	0	Government Publications Grant (through the Royal Society)	3,500	0	0		
43,750	0	0	The Chemical Council	16,600	0	0		
							20,100	0 0
		49,550	0 0					
		5	0 0	Donation			10	0
				Transfer from General Purposes Account			18,081	16 2
		13,656	2 10					
		£86,385	0 5				£70,171	18 8

1952			*Expenditure.*	1953				
£	s.	d.		£	s.	d.	£	s. d.
			Expenses on account of Journal:					
5,406	6	0	Salaries, Wages, Superannuation, etc.	5,831	1	2		
26,021	12	8	Printing	22,922	5	5		
12,492	2	2	Paper	7,041	4	1		
4,589	2	11	Banding and Distribution	3,932	6	6		
3,770	8	5	Authors' Reprints	3,403	7	5		
8	5	0	Furniture	387	4	5		
308	0	5	Office Expenses and Stationery ...	241	6	7		
197	18	2	Postages	201	15	5		
152	11	8	Travelling Expenses	162	10	5		
492	8	11	Miscellaneous	419	7	2		
							44,542	8 7
		53,438	16 4					
			Annual Reports on the Progress of Chemistry				3,763	6 9
		3,499	6 1	Quarterly Reviews			3,674	11 10
		3,446	18 0	Current Chemical Papers (Preliminary Expenses)			391	11 6
		—	— —	Bureau of Abstracts:				
		26,000	0 0	Balance of Grants 1952, 1953	15,800	0	0	
		—	— —	Provision for Final Liability	2,000	0	0	
							17,800	0 0
		£86,385	0 5				£70,171	18 8

Income and Expenditure Accounts for the Year ended 31st December, 1953.

LIBRARY.

1952			*Income.*	1953		
£	s.	d.		£	s.	d.
			Contributions for Books, Periodicals, Binding, Fittings, and Furniture:			
2,453	1	8	Transfer from General Purposes Account...	2,490	0	1
			Contributions towards maintenance through the Chemical Council:			
842	0	5	Chemical Society (General Purposes Account)	912	10	10
1,912	5	3	Royal Institute of Chemistry	2,069	5	9
704	6	3	Society of Chemical Industry	679	1	1
196	14	9	Faraday Society	248	9	9
133	15	6	Society for Analytical Chemistry	128	10	6
145	11	8	Biochemical Society	246	6	11
599	11	0	Chemical Council (Direct Grant)	711	13	11
4,534	4	10		4,995	18	9
			Contributions from other sources:			
100	0	0	Association of British Chemical Manufacturers	100	0	0
50	0	0	Institute of Brewing	50	0	0
10	10	0	Society of Dyers and Colourists	10	10	0
22	10	6	Miscellaneous	19	15	1
183	0	6		180	5	1
£7,170	7	0		£7,666	3	11

1952			*Expenditure.*	1953		
£	s.	d.		£	s.	d.
			Capital Expenditure:			
1,893	2	3	Books and Periodicals *	1,213	13	6
486	3	6	Binding...	1,199	18	2
73	15	11	Furniture	76	8	5
2,453	1	8		2,490	0	1
			Maintenance:			
4,102	1	0	Salaries, Wages, Superannuation, etc. ...	4,551	1	1
70	0	8	Postages	73	2	7
312	7	9	House Expenses, etc....	365	15	0
210	2	10	Office Expenses and Stationery	164	4	7
22	13	1	Miscellaneous	22	0	7
4,717	5	4		5,176	3	10
£7,170	7	0		£7,666	3	11

* Other than those received in exchange.

INCOME AND EXPENDITURE ACCOUNTS FOR THE YEAR ENDED 31ST DECEMBER, 1953.

SPECIAL RESERVE FUND.

1952	*Income.*	1953	1952	*Expenditure.*	1953
£ s. d.		£ s. d.	£ s. d.		£ s. d.
161 7 9	Dividends on Investments	216 3 6		Balance, being Excess of Income over Expenditure, carried to Balance	
25 13 4	Deposit Interest	201 12 0	187 1 1	Sheet	417 15 6
£187 1 1		£417 15 6	£187 1 1		£417 15 6

SPECIAL PUBLICATIONS FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
2,550 7 2	Sales of Publications and Royalties received	301 13 0	44 10 4	Cost of Publications	215 13 5
69 18 2	Dividends on Investments	69 18 2	21 18 8	Miscellaneous	17 7 8
34 8 9	Deposit Interest	77 1 7		Balance, being Excess of Income over Expenditure, carried to Balance	
			2,588 5 1	Sheet	215 11 8
£2,654 14 1		£448 12 9	£2,654 14 1		£448 12 9

STAFF PENSIONS FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
800 0 0	Transfer from General Purposes Account and Refund of Premiums	2,049 8 10	965 0 0	Pensions	807 8 4
89 12 9	Dividends on Investments	81 17 4	4 15 0	Miscellaneous	4 14 9
5 8 0	Deposit Interest	12 18 4		Balance, being Excess of Income over Expenditure, carried to Balance	
	Balance, being Excess of Expenditure over Income, carried to Balance		— — —	Sheet	1,332 1 5
74 14 3	Sheet	— — —			
£969 15 0		£2,144 4 6	£969 15 0		£2,144 4 6

Income and Expenditure Accounts for the Year ended 31st December, 1953.

CENTENARY FUND.

1952	*Income.*	1953	1952	*Expenditure.*	1953
£ s. d.		£ s. d.	£ s. d.		£ s. d.
654 0 7	Dividends on Investments...	825 4 7	166 2 2	Expenses of Lecturers & Delegates	712 13 5
			32 14 0	Miscellaneous	41 5 2
			455 4 5	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	71 6 0
£654 0 7		£825 4 7	£654 0 7		£825 4 7

CORDAY-MORGAN MEDAL AND PRIZE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
275 4 4	Dividends on Investments...	283 13 2	157 10 0	Prize	157 10 0
1 15 3	Deposit Interest	1 18 6	7 10 0	Medal	7 10 0
			29 16 2	Miscellaneous	29 6 7
			82 3 5	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	91 5 1
£276 19 7		£285 11 8	£276 19 7		£285 11 8

CORDAY-MORGAN MEMORIAL FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
506 8 10	Dividends on Investments...	531 9 1	400 0 0	Grant to the Corday-Morgan Memorial Fund Executive	400 0 0
			2 14 6	Memorial Expenses (Clause 12 of the Will)	4 10 0
			27 15 8	Miscellaneous	26 2 8
			75 18 8	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	100 16 5
£506 8 10		£531 9 1	£506 8 10		£531 9 1

Income and Expenditure Accounts for the Year ended 31st December, 1953.

FARADAY LECTURE FUND.

1952	*Income.*	1953	1952	*Expenditure.*	1953
£ s. d.		£ s. d.	£ s. d.		£ s. d.
15 8 8	Dividend on Investment	15 8 8	— — —	Honorarium	26 5 0
— — —	Balance, being Excess of Expenditure over Income, carried to Balance Sheet	15 14 9	— — —	Faraday Medal	4 3 0
			15 5	Miscellaneous	15 5
			14 13 3	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	— — —
£15 8 8		£31 3 5	£15 8 8		£31 3 5

ROBERT JOHN FLINTOFF TRUST.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
34 13 8	Dividends on Investments	34 13 8	1 14 8	Miscellaneous	1 14 8
			32 19 0	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	32 19 0
£34 13 8		£34 13 8	£34 13 8		£34 13 8

EDWARD FRANK HARRISON MEMORIAL TRUST.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
46 16 10	Dividends on Investments	46 16 10	2 6 10	Miscellaneous	24 14 10
			44 10 0	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	22 2 0
£46 16 10		£46 16 10	£46 16 10		£46 16 10

INCOME AND EXPENDITURE ACCOUNTS FOR THE YEAR ENDED 31ST DECEMBER, 1953.

RESEARCH FUND.

1952	*Income.*	1953	1952	*Expenditure.*	1953
£ s. d.		£ s. d.	£ s. d.		£ s. d.
749 16 0	Dividends on Investments	749 16 0	643 5 0	Grants awarded	734 14 6
6 6	Deposit Interest	6 6	21 0 0	Honorarium, Hugo Müller Lecture	— — —
22 9 10	Grants repaid or not claimed	63 0 5	71 6 4	Miscellaneous	52 19 7
10 11 10	Miscellaneous	— — —			
			47 12 10	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	25 8 10
£783 4 2		£813 2 11	£783 4 2		£813 2 11

SPECIAL LECTURES FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
50 1 10	Dividend on Investment	50 1 10	— — —	Honorarium	26 5 0
			2 10 1	Miscellaneous	2 10 1
			47 11 9	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	21 6 9
£50 1 10		£50 1 10	£50 1 10		£50 1 10

TILDEN LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
67 10 8	Dividends on Investments	71 5 0	31 10 0	Honoraria	31 10 0
10 6	Deposit Interest	11 6	3 18 6	Lecture Expenses	— — —
			3 8 0	Miscellaneous	3 11 10
			29 4 8	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	36 14 8
£68 1 2		£71 16 6	£68 1 2		£71 16 6

THE CHEMICAL SOCIETY

BALANCE SHEETS, 31st December, 1953.

GENERAL PURPOSES.

1952 £	1952 s.	1952 d.	*Liabilities.*	1953 £	1953 s.	1953 d.	1953 £	1953 s.	1953 d.
			Sundry Creditors:						
10,993	6	2	Printing and Miscellaneous	18,790	3	9			
13,628	4	3	Fellowship Subscriptions in advance	12,864	0	10			
12,968	19	9	Publications sold in advance	14,057	11	5			
—	—	—	Special Reserve Fund...	5,500	0	0			
—	—	—	Staff Pensions Fund	1,200	0	0			
444	1	6	Provision for Special Purposes	400	0	0			
							52,811	16	0
			Excess of Assets over Liabilities as per last Balance Sheet	27,021	9	3			
24,126	12	7	*Add* Life Composition Fees	180	0	0			
381	5	0	Excess of Income over Expenditure for year	291	16	2			
2,513	11	8							
27,021	9	3		27,493	5	5			
			Net loss on change of Investments...	764	16	0			
—	—	—	*Deduct* transfer from Special Reserve Fund	764	16	0	—	—	—
		27,021	9	3			27,493	5	5
		£65,056	0	11			£80,305	1	5

1952 £	1952 s.	1952 d.	*Assets.*	1953 £	1953 s.	1953 d.
29,156	2	6	Investments as per Schedule (cost or value when acquired)	28,391	6	6
17,785	15	5	Sundry Debtors	13,625	12	1
3,122	7	11	Stock of Paper (Journal, Annual Reports, Quarterly Reviews and Current Chemical Papers)	3,922	18	8
14,991	15	1	Cash at Bank (including Deposit) and in hand	34,365	4	2
£65,056	0	11		£80,305	1	5

Balance Sheets, 31st December, 1953.

PUBLICATIONS FUND.

1952	*Liabilities.*	1953	1952	*Assets.*	1953
£ s. d.		£ s. d.	£ s. d.		£ s. d.
8 11 0	Sundry Creditors	8 2 0	8 11 0	Sundry Debtors	8 2 0
10,978 19 7	Excess of Assets over Liabilities as per last Balance Sheet	10,978 19 7	10,978 19 7	Investments as per Schedule (cost or value when acquired)	10,978 19 7
£10,987 10 7		£10,987 1 7	£10,987 10 7		£10,987 1 7

SPECIAL RESERVE FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.
— — —		Sundry Creditors	764 16 0	13 3 11	Sundry Debtors	5,512 10 1
		Publications Reserve:		7,816 9 5	Investments as per Schedule (cost or value when acquired)	7,816 9 5
9,585 0 7	9,585 0 7	As per last Balance Sheet		10,904 10 10	Cash at Bank and on Deposit in London Trustee Savings Bank	11,324 0 2
— — —	3,000 0 0	*Add* Transfer from General Purposes Account	12,585 0 7			
		Library Reserve:				
1,309 17 8		As per last Balance Sheet	1,309 17 8			
		Building and Equipment Reserve:				
3,025 0 0	3,025 0 0	As per last Balance Sheet				
— — —	1,000 0 0	*Add* Transfer from General Purposes Account	4,025 0 0			
		Investments Reserve:				
2,100 0 0	2,100 0 0	As per last Balance Sheet				
— — —		*Deduct* Transfer to General Purposes Account—net loss on Change of Investments	764 16 0			
	1,335 4 0					
— — —	1,500 0 0	*Add* Transfer from General Purposes Account	2,835 4 0			
		General Purposes Reserve:				
2,527 4 10	2,714 5 11	Amount brought forward				
— — —	1 0 0	*Add* Premium on Conversion of Stock				
187 1 1	417 15 6	Excess of Income over Expenditure for year	3,133 1 5			
2,714 5 11						
£18,734 4 2			£24,652 19 8	£18,734 4 2		£24,652 19 8

BALANCE SHEETS, 31ST DECEMBER, 1953.

SPECIAL PUBLICATIONS FUND.

1952 £ s. d.	1952 £ s. d.	*Liabilities.*	1953 £ s. d.	1953 £ s. d.	1952 £ s. d.	*Assets.*	1953 £ s. d.
	62 4 3	Sundry Creditors		62 4 5	47 2 5	Sundry Debtors	105 11 9
3,385 2 9		Excess of Assets over Liabilities as per last Balance Sheet	5,973 7 10		2,011 19 10	Investments as per Schedule (cost or value when acquired)	2,011 19 10
2,588 5 1		*Add* Excess of Income over Expenditure for year	215 11 8		3,976 9 10	Cash at Bank and on deposit in the Post Office Savings Bank and London Trustee Savings Bank	4,133 12 4
	5,973 7 10			6,188 19 6			
	£6,035 12 1			£6,251 3 11	£6,035 12 1		£6,251 3 11

STAFF PENSIONS FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.		£ s. d.
	4 15 0	Sundry Creditors		41 14 9	— — —	Sundry Debtor	1,200 0 0
4,056 5 8		Excess of Assets over Liabilities as per last Balance Sheet	5,981 11 5		3,722 3 10	Investments as per Schedule (cost or value when acquired)	3,572 3 10
74 14 3		*Deduct* Excess of Expenditure over Income for year	— — —		264 2 7	Cash at Bank and on deposit in the Post Office Savings Bank	583 3 9
— — —		*Add* Excess of Income over Expenditure for year	1,332 1 5				
	3,981 11 5			5,313 12 10			
	£3,986 6 5			£5,355 7 7	£3,986 6 5		£5,355 7 7

CENTENARY FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.		£ s. d.
	56 10 8	Sundry Creditors		61 19 11	400 13 1	Sundry Debtors	412 3 4
		Capital Account :			23,198 3 4	Investments as per Schedule (cost or value when acquired)	27,698 3 4
22,977 11 1		As per last Balance Sheet	25,531 1 0		2,034 15 10	Cash at Bank	145 1 9
2,553 9 11		*Add* Contributions under Deeds and Donations for year	2,545 0 11				
	25,531 1 0			28,076 1 11			
— — —		Income Account :					
		Amount brought forward	46 0 7				
455 4 6		*Add* Excess of Income over Expenditure for year	71 6 0				
409 3 10		*Deduct* deficit brought forward	— — —				
	46 0 7			117 6 7			
	£25,633 12 3			£28,255 8 5	£25,633 12 3		£28,255 8 5

BALANCE SHEETS, 31ST DECEMBER, 1953.

CORDAY-MORGAN MEDAL AND PRIZE FUND.

1952			*Liabilities.*			1953			1952			*Assets.*			1953		
£	s.	d.		£	s.	d.	£	s. d.	£	s.	d.		£	s. d.	£	s.	d.
			Sundry Creditors				80	19 2	73	16	1	Sundry Debtors			65	2	8
			Capital Account :						6,858	3	2	Investments as per Schedule (cost or value when acquired)			6,858	3	2
5,887	10	9	As per last Balance Sheet	5,885	9	8			474	19	5	Cash at Bank (including Deposit			642	1	11
			Add Balance on Bonus Issue of Imperial Tobacco Co. (G.B. & I.) Ltd. Ordinary Stock	—	—												
	10	6															
5,888	1	3															
2	11	7	*Deduct* Loss on Repayment of Investment	—	—	—											
							5,885	9 8									
			Income Account :														
1,381	15	4	As per last Balance Sheet	1,507	13	10											
43	15	1	*Add* Income Tax recovered	—	—	—											
82	3	5	Excess of Income over Expenditure for year	91	5	1											
							1,598	18 11									
							£7,565	7 9									
									£7,406	18	8				£7,565	7	9

CORDAY-MORGAN MEMORIAL FUND.

£	s.	d.		£	s.	d.	£	s. d.	£	s.	d.		£	s. d.	£	s.	d.
			Sundry Creditors				31	1 5	120	10	0	Sundry Debtors			170	1	1
			Capital Account :						12,232	1	5	Investments as per Schedule (cost or value when acquired)			12,232	1	5
		10,090	2 8	As per last Balance Sheet	10,090	2	8		445	16	5	Cash at Bank			499	9	5
		— — —	*Add* Balance on Bonus Issue of Barclays Bank Ltd., "B" Ordinary Stock	1	16	5											
							10,091	19 1									
			Income Account :														
2,512	19	4	As per last Balance Sheet	2,677	15	0											
88	17	0	*Add* Income Tax recovered	—	—	—											
75	18	8	Excess of Income over Expenditure for year	100	16	5											
		2,677	15 0				2,778	11 5									
		£12,798	7 10				£12,901	11 11	£12,798	7	10				£12,901	11	11

BALANCE SHEETS, 31ST DECEMBER, 1953.

FARADAY LECTURE FUND.

1952			*Liabilities.*	1953			1952			*Assets.*	1953		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			Sundry Creditors		15	5	439	4	0	Investment as per Schedule (cost or value when acquired)	439	4	0
487	10	1	Excess of Assets over Liabilities as per last Balance Sheet	502	3	4	63	14	9	Cash at Bank	48	0	0
14	13	3	*Add* Excess of Income over Expenditure for year	—	—	—							
—	—	—	*Deduct* Excess of Expenditure over Income for year	15	14	9							
		502	3	4		486	8	7					
		£502	18	9		£487	4	0	£502	18	9		£487	4	0

ROBERT JOHN FLINTOFF TRUST.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.	
			1	14	8	Sundry Creditors				5	2	0	Sundry Debtors ... ...
1,045	1	6				Excess of Assets over Liabilities as per last Balance Sheet	1,078	0	6	1,000	0	0	Investments as per Schedule (cost or value when acquired) ... ...
32	19	0				*Add* Excess of Income over Expenditure for year	32	19	0	74	13	2	Cash at Bank ... ...
		1,078	0	6			1,110	19	6				
		£1,079	15	2			£1,112	14	2	£1,079	15	2	

£	s.	d.	£	s.	d.
			5	2	0
			1,000	0	0
			107	12	2
			£1,112	14	2

EDWARD FRANK HARRISON MEMORIAL TRUST.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.	
			2	6	10	Sundry Creditors				1,101	7	11	Investments as per Schedule (cost or value when acquired) ... ...
1,137	15	8				Excess of Assets over Liabilities as per last Balance Sheet	1,182	5	8	83	4	7	Cash at Bank ... ...
44	10	0				*Add* Excess of Income over Expenditure for year	22	2	0				
		1,182	5	8			1,204	7	8				
		£1,184	12	6			£1,206	14	6	£1,184	12	6	

£	s.	d.
1,101	7	11
105	6	7
£1,206	14	6

BALANCE SHEETS, 31ST DECEMBER, 1953.

RESEARCH FUND.

1952			*Liabilities.*	1953			1952			*Assets.*	1953		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			Sundry Creditors							Sundry Debtors			
		793 0 4				824 18 7	48 1 3				27 0 0		
			Excess of Assets over Liabilities as per				23,923 4 7			Investments as per Schedule (cost or value when acquired)	23,923 4 7		
23,909 5 6			last Balance Sheet	23,956 18 4			778 12 10			Cash at Bank and on deposit in Post Office Savings Bank	857 1 2		
			Add Excess of Income over Expendi-										
47 12 10			ture for year	25 8 10									
		23,956 18 4				23,982 7 2							
		£24,749 18 8				£24,807 5 9	£24,749 18 8				£24,807 5 9		

SPECIAL LECTURES FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			2 10 1			Sundry Creditors				2 10 1				1,615 5 0		Investment as per Schedule (cost or value when acquired)	1,615 5 5
						Excess of Assets over Liabilities as per last								89 13 8		Cash at Bank	111 0 0
1,654 16 10						Balance Sheet	1,702 8 7										
						Add Excess of Income over Expenditure											
47 11 9						for year	21 6 9										
		1,702 8 7								1,723 15 4							
		£1,704 18 8								£1,726 5 5				£1,704 18 8			£1,726 5 5

TILDEN LECTURE FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			3 8 0			Sundry Creditors				3 11 10				9 15 2		Sundry Debtors	10 1 7
						Excess of Assets over Liabilities as per last								1,878 14 10		Investments as per Schedule (cost or value when acquired)	1,878 14 10
1,994 13 7						Balance Sheet	2,023 18 3							138 16 3		Cash at Bank (including Deposit)	175 8 4
						Add Excess of Income over Expenditure											
29 4 8						for year	36 14 8										
		2,023 18 3								2,060 12 11							
		£2,027 6 3								£2,064 4 9				£2,027 6 3			£2,064 4 9

SCHEDULE OF INVESTMENTS.

GENERAL PURPOSES.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1953.* £ s. d.
£2,609 14*s.* 4*d.* 3½% Conversion Loan, 1961, or after	2,044 16 0	2,244 7 1
£2,000 3% Savings Bonds, 1965/75	2,006 4 5	1,790 0 0
£1,000 3½% Defence Bonds	1,000 0 0	1,000 0 0
£200 3% Defence Bonds, 3rd Issue	199 7 0	200 0 0
£4,747 4*s.* 5*d.* 3% British Transport Guaranteed Stock, 1978/88	5,704 9 8	4,011 8 1
£2,546 1*s.* 4*d.* 3% British Electricity Guaranteed Stock, 1968/73	2,549 4 5	2,278 14 7
£2,425 8*s.* 9*d.* 3% Commonwealth of Australia Registered Stock, 1964/66	2,434 10 8	2,231 8 0
£A3,000 3½% Commonwealth of Australia Treasury Bonds, 1961/64	2,552 16 7	2,160 0 0
£1,000 4% Canadian Pacific Railway Perp. Deb. Stock	838 8 9	850 0 0
£766 3½% London Trust Co., Ltd., Red. Deb. Stock	576 2 9	555 7 0
£1,000 5% Distillers Co., Ltd., Unsec. Loan Stock	1,066 14 3	1,040 0 0
500 8% Anglo-Iranian Oil Co., Ltd., Cum. First Pref. £1 Stock Units	778 16 6	800 0 0
1,000 5% Bell London & Provincial Props. Ltd., Cum. Pref. £1 Shares	884 1 6	1,050 0 0
900 6½% J. & N. Phillips & Co., Ltd., Cum. Pref. £1 Shares	929 14 0	933 15 0
1,000 5% Geo. Sandeman & Sons, Ltd., Cum. Pref. £1 Shares	938 1 6	987 10 0
160 Allen & Hanbury, Ltd., Ord. £1 Shares	521 6 6	440 0 0
£400 Cable & Wireless (Holdings), Ltd., Ordinary Stock	549 6 6	584 0 0
50 Commercial Union Assurance Co., Ltd., £1 Stock Units	580 12 6	625 0 0
400 Goodlass Wall & Lead Industries, Ltd., Ord. 10*s.* Stock Units	496 9 6	560 0 0
120 Leyland Motors, Ltd., Ordinary £1 Shares	570 6 6	501 0 0
150 Shell Transport and Trading Co., Ltd., Ord. £1 Stock Units	665 12 6	735 18 0
160 Peninsular and Orient Steam Navigation Co., Ltd., Deferred £1 Stock Units	504 4 6	496 0 0
	£28,391 6 6	£26,074 7 9

PUBLICATIONS FUND.

£2,260 19*s.* 9*d.* 3½% Conversion Loan, 1961, or after	1,566 16 4	1,944 9 0
£1,000 3% Savings Bonds, 1955/65	1,000 0 0	975 0 0
£2,261 1*s.* 11*d.* 3% Savings Bonds, 1960/70	2,276 1 11	2,068 18 0
£2,175 13*s.* 4*d.* 3% British Transport Guaranteed Stock, 1978/88	1,929 1 4	1,838 8 9
£2,000 3% British Electricity Guaranteed Stock, 1968/73	2,002 10 0	1,790 0 0
£1,200 3% Commonwealth of Australia Registered Stock, 1964/66	1,204 10 0	1,104 0 0
£982 12*s.* 0*d.* 3% Southern Rhodesia Stock, 1971/73	1,000 0 0	840 2 5
	£10,978 19 7	£10,560 18 2

SPECIAL RESERVE FUND.

£1,165 2½% Funding Loan, 1956/61	1,169 7 5	1,141 14 0
£2,223 5*s.* 0*d.* 2½% National War Bonds, 1954/56	2,210 17 0	2,228 11 2
£1,700 3% Defence Bonds, 3rd Issue	1,689 15 0	1,700 0 0
£100 3½% Defence Bonds (Conversion Issue)	99 8 0	100 0 0
£2,582 10*s.* 9*d.* 3% Liverpool Corporation Stock, 1955/58	2,647 2 0	2,556 14 3
	£7,816 9 5	£7,726 19 5

SPECIAL PUBLICATIONS FUND.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1953.* £ s. d.
£715 8*s.* 10*d.* 3½% Conversion Loan, 1961, or after	541 2 4	615 5 7
£746 1*s.* 0*d.* 3% British Transport Guaranteed Stock, 1978/88	719 18 9	630 8 3
£750 3% British Electricity Guaranteed Stock, 1968/73	750 18 9	671 5 0
	£2,011 19 10	£1,916 18 10

STAFF PENSIONS FUND.

£114 1*s.* 11*d.* 3½% Conversion Loan, 1961, or after	88 2 3	98 2 5
£170 3% Savings Bonds, 1955/65	170 0 0	165 15 0
£815 2*s.* 7*d.* 2½% Funding Loan, 1956/61	818 3 9	798 16 6
£1,505 3% Defence Bonds, 3rd Issue	1,495 17 10	1,505 0 0
£1,000 3½% Defence Bonds	1,000 0 0	1,000 0 0
	£3,572 3 10	£3,567 13 11

CENTENARY FUND.

£2,637 10*s.* 6*d.* 3½% Conversion Loan, 1961, or after	2,300 0 0	2,268 5 5
£2,477 13*s.* 11*d.* 3% Savings Bonds, 1955/65	2,491 11 10	2,415 15 0
£2,500 3% Savings Bonds, 1960/70	2,534 7 6	2,287 10 0
£2,705 18*s.* 7*d.* 2½% Savings Bonds, 1964/67	2,500 0 0	2,448 17 4
£2,279 13*s.* 0*d.* 3% British Transport Guaranteed Stock, 1978/88	2,237 7 9	1,926 6 1
£2,500 3% British Electricity Guaranteed Stock, 1968/73	2,498 8 9	2,237 10 0
£4,933, 15*s.* 11*d.* 4% Consolidated Stock, 1957, or after	4,500 0 0	4,613 2 0
£2,302 19*s.* 6*d.* 3½% Agricultural Mortgage Corporation Deb. Stock, 1975/78	2,000 0 0	2,015 2 1
£1,970 1*s.* 0*d.* 3% New Zealand Stock, 1973/77	2,000 0 0	1,704 1 10
£1,716 15*s.* 2*d.* 3½% Northern Ireland Stock, 1969/71	1,700 0 0	1,553 13 4
£A3,500 3½% Commonwealth of Australia Treasury Bonds, 1961/64	2,936 7 6	2,520 0 0
	£27,698 3 4	£25,990 3 1

CORDAY-MORGAN MEDAL AND PRIZE FUND.

£1,398 5*s.* 4*d.* 3½% War Stock, 1952, or after	1,325 14 0	1,185 0 7
£635 3*s.* 10*d.* 3% British Transport Guaranteed Stock, 1978/88	574 17 0	536 14 9
£207 1*s.* 10*d.* 4½% British Electricity Guaranteed Stock, 1974/79	206 5 0	215 7 6
£206 5*s.* 0*d.* 4% Consolidated Stock, 1957, or after	213 9 4	192 16 10
£774 6*s.* 3*d.* 3% British Guiana Government Stock, 1975/80	690 5 4	631 1 4
£137 10*s.* 0*d.* 3% Federated Malay States Government Stock, 1960/70	120 6 3	115 10 0
£137 10*s.* 0*d.* 3½% Bournemouth Corporation Stock Red., 1958/62	133 14 5	136 2 6
£206 5*s.* 0*d.* 4½% Hertfordshire County Red. Stock, 1955/65	215 0 4	210 9 6
£300 3½% Hertfordshire County Red. Stock, 1954/59	297 15 0	303 0 0
112 Barclays Bank (D. C. & O.) Ltd., "A" Ordinary £1 Stock Units	201 7 6	221 4 0
172 Mitchells & Butlers, Ltd., Ordinary £1 Stock Units	713 16 0	462 5 0
206 Watney, Combe & Reid, Ltd., Deferred Ordinary £1 Shares	597 8 0	602 11 0
83 Imperial Tobacco Co. (G.B. & I.) Ltd., Ordinary £1 Shares	263 5 0	238 12 6
£240 Cardinal Investment Trust, Ltd., 3½% Convertible Debenture Stock	291 0 0	258 16 0
104 Commercial Union Assurance Co., Ltd., Ordinary £1 Stock Units	1,014 0 0	1,300 0 0
	£6,858 3 2	£6,609 11 6

SCHEDULE OF INVESTMENTS.

CORDAY–MORGAN MEMORIAL FUND.

Nominal Details.	*Cost or Value when Acquired.*	*Market Value 31st December, 1953.*
	£ s. d.	£ s. d.
£1,530 2s. 5d. 3½% Conversion Loan, 1961, or after	1,426 4 2	1,315 18 1
£1,973 16s. 11d. 3½% War Stock, 1952, or after	1,880 1 10	1,672 16 8
£477 1s. 10d. 3% British Electricity Guaranteed Stock, 1968/73 ...	450 17 0	427 0 0
£1,062 10s. 11d. 3% British Gas Guaranteed Stock, 1990/95	894 5 7	908 9 6
£217 12s. 6d. 3% London County Consolidated Stock, 1962/67 ...	208 7 6	201 6 1
£1,035 0s. 7d. 3% Redemption Stock, 1986/96	928 18 10	879 15 6
£137 10s. 0d. 4½% Kenya Government Stock, 1961/71	148 16 11	137 10 0
£300 3% New Zealand Government Stock, 1952/55	298 10 0	300 0 0
£1,000 4% South Staffordshire Waterworks Red. Preference Stock, 1971	1,046 10 6	925 0 0
£300 4½% Hull Corporation Stock, 1952/72	303 15 0	300 0 0
£412 10s. 0d. 3% City of Plymouth Stock, 1954	405 5 7	416 12 6
108 Barclays Bank, Ltd., "B" Ordinary £1 Stock Units	237 3 0	245 14 0
206 Benskins Watford Brewery, Ltd., Ordinary £1 Shares	684 19 0	824 0 0
206 H. & G. Simmonds, Ltd., Ordinary £1 Stock Units	824 0 0	515 0 0
160 Imperial Tobacco (G.B. & I.) Ltd., Ordinary £1 Shares	506 5 0	460 0 0
108 Thomas Tilling & Co., Ltd., Ordinary £1 Stock Units	107 6 6	175 10 0
£340 Alliance Trust, Ltd., 4½% Debenture Stock, 1956	344 5 0	324 14 0
69 London & Lancashire Insurance Co., Ltd., Ordinary £1 Stock Units	448 10 0	504 11 3
68 Phœnix Assurance Co., Ltd., Ordinary £1 Stock Units	1,088 0 0	1,351 10 0
	£12,232 1 5	£11,885 7 7

FARADAY LECTURE FUND.

£441 1s. 11d. 3½% Conversion Loan, 1961, or after	£439 4 0	£379 6 10

ROBERT JOHN FLINTOFF TRUST.

£523 2s. 2d. 3½% Conversion Loan, 1961, or after	500 0 0	449 17 5
£545 19s. 4d. 3% British Transport Guaranteed Stock, 1978/88 ...	500 0 0	461 6 10
	£1,000 0 0	£911 4 3

EDWARD FRANK HARRISON MEMORIAL TRUST.

Nominal Details.	*Cost or Value when Acquired.*	*Market Value 31st December, 1953.*
	£ s. d.	£ s. d.
£61 15s. 8d. 3½% Conversion Loan, 1961, or after	50 1 5	53 2 8
£1,489 10s. 6d. 3% British Transport Guaranteed Stock, 1978/88 ...	1,051 6 6	1,258 12 11
	£1,101 7 11	£1,311 15 7

RESEARCH FUND.

£4,177 16s. 1d. 3½% Conversion Loan, 1961, or after	3,625 16 8	3,592 18 3
£500 3% Defence Bonds, 4th issue	500 0 0	500 0 0
£1,835 2½% Funding Loan, 1956/61	1,835 0 0	1,798 6 0
£1,500 3% Savings Bonds, 1955/65	1,515 0 0	1,462 10 0
£4,000 3% Savings Bonds, 1960/70	4,060 0 0	3,660 0 0
£3,755 2s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	3,567 19 5	3,173 1 3
£3,719 8s. 2d. 3% British Electricity Guaranteed Stock, 1968/73 ...	3,724 1 2	3,328 17 5
£4,000 3% Commonwealth of Australia Registered Stock, 1964/66 ...	4,015 0 0	3,680 0 0
£1,116 7s. 0d. 3% New Zealand Stock, 1973/77	1,080 7 4	965 12 10
	£23,923 4 7	£22,161 5 9

SPECIAL LECTURES FUND

£1,669 17s. 3d. 3% British Transport Guaranteed Stock, 1978/88 ...	£1,615 5 0	£1,411 0 8

TILDEN LECTURE FUND.

£419 4s. 10d. 3% Funding Loan, 1959/69	386 12 10	389 17 11
£681 19s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	625 2 0	576 5 0
186 National Provincial Bank Shares £5 each, £1 paid "B"	678 18 0	734 14 0
£220 3% Metropolitan Water Board (Kent Water Works) Deb. Stock	188 2 0	162 16 0
	£1,878 14 10	£1,863 12 11

W. A. AKERS, *Treasurer.*

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers of the Society, and certify them to be in accordance therewith and, in our opinion, correct. We have also verified the Balances at the Bankers and Investments.

FINSBURY CIRCUS HOUSE,
BLOMFIELD STREET, E.C.2
25th MARCH, 1954.

W. B. KEEN & CO.
Chartered Accountants.

BYE-LAWS OF THE CHEMICAL SOCIETY

Adopted
at the Annual General Meeting held in Manchester
on Friday, April 2nd, 1954

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THE CHEMICAL SOCIETY

BYE-LAWS

Part I.—*The Election, Admission and Privileges of, and Payments by, Fellows.*

1. Fellows shall be elected by the Council. Fellows may be of either sex. In these Bye-Laws, unless there be something in the context or subject inconsistent therewith, words importing males shall include females.

2. Every candidate for election into the Society as a Fellow thereof shall be proposed to the Council in writing by not less than two Fellows of the Society to whom he is personally known. The proposals shall be in such form as the Council may from time to time prescribe, and shall be signed by all the proposers. Provided that in the case of a candidate resident abroad unable to obtain the signatures of two Fellows as aforesaid, the Council shall have power to accept a proposal signed by one Fellow of the Society to whom the candidate is personally known as equivalent to a proposal signed by two Fellows as aforesaid.

3. The application of a candidate for election shall be accompanied by a deposit covering the admission fee, if any, or such part thereof as may be required by the Council, and the first annual subscription, which deposit shall be returned to the candidate in the event of non-election.

4. Each candidate for election shall sign and send to the Honorary Secretaries the following form of obligation:

> " I, the undersigned, do hereby engage that, if elected to the Fellowship, I will endeavour to promote the interests and welfare of the Chemical Society and I will observe its laws and to the utmost of my power maintain its dignity as long as I shall continue a Fellow thereof."

Signature of this obligation shall record his acquiescence in all the rules, regulations, and laws of the Society, and pledge him to their due observance.

5. The name of the candidate and such other particulars concerning him as the Council may from time to time prescribe shall be published in the Society's *Proceedings* not less than ten days prior to the meeting of the Council at which his application for election is first considered by the Council, and the proposal form shall also be kept available in the Society's Rooms for inspection by Fellows for not less than ten days immediately prior to such meeting.

6. The provisions of Bye-Law 60 as to the ordinary mode of decision on questions before the Council shall apply to elections of Fellows, but a proposer, being a member of the Council, may be present during any discussion concerning, and may vote upon the election of, any candidate proposed by him.

7. The Honorary Secretaries shall in writing inform every candidate of the Council's decision upon his application.

8. The formal admission of Fellows shall take place at Scientific Meetings of the Society. After the reading aloud by one of the Officers of the prescribed form of obligation, the Fellow to be admitted shall subscribe his name to the obligation in the Charter-book, and be introduced by the Chairman, who, taking him by the hand, shall say: " ——, I do, by the authority and in the name of the Chemical Society, admit you a Fellow thereof."

9. (i) The amount of the admission fee, if any, payable on election to Fellowship, and the amount of the annual subscription payable by any Fellow shall be determined by the Council from time to time subject to confirmation by a General Meeting of the Society. Provided that the Council shall have power without such or any confirmation and whenever it may consider it desirable to do so:

> (*a*) Either wholly to remit or to reduce the admission fee or to permit its payment by instalments.
>
> (*b*) Either wholly to remit or to reduce the annual subscription payable by any person who has been a Fellow for not less than forty years.

Provided further that the Council shall have power subject to confirmation by a General Meeting :

(*c*) To reduce to such extent and in respect of such year or years as the Council may from time to time determine the annual subscription payable by Fellows resident in any British Dominion, Colony, possession or mandated territory.

(ii) The amount of the life composition fee shall be such sum as the Council may from time to time determine.

10. The annual subscription to be paid by Fellows shall become due on the first day of January in every year, but a candidate elected during the month of October, November, or December shall not be required to pay the subscription for the current year unless he desires to purchase the publications of the Society issued to Fellows for that year.

11. (i) Every Fellow shall have the right to be present and to vote at all meetings of the Society, and to propose candidates for election into the Society, and he shall be entitled, so long as his annual subscription be not in arrear and on payment of such charges and under such conditions, if any, as the Council may from time to time prescribe, to be supplied with publications of the Society. Provided that the Council may supply Fellows under twenty-seven years of age with copies of publications of the Society without making any charge therefor or at a reduced charge, as may be determined by the Council.

(ii) Every Fellow shall also be entitled to use the books in the Society's Library under such regulations as the Council, upon the recommendation of the Joint Library Committee referred to in Bye-Law 66, may from time to time deem advisable, and shall have the privilege of introducing to Scientific Meetings of the Society two visitors whose names shall be entered in a book kept for that purpose, together with the name of the Fellow introducing such visitors.

Part II.—*Honorary Fellows.*

12. The Council shall have power at any time and from time to time to elect to membership of the Society as Honorary Fellows thereof any person of either sex, whether British or foreign, distinguished in chemical science or whom for any other sufficient reason the Council may consider it desirable to admit to honorary membership of the Society. Provided that the number of Honorary Fellows shall not at any time exceed forty.

13. Persons proposed to be admitted as Honorary Fellows shall be nominated at one meeting of the Council, and the proposal shall be voted upon at a subsequent meeting of the Council. The name of the candidate and such other particulars concerning him as the Council may from time to time prescribe shall be published in the Society's *Proceedings* not less than ten days prior to the meeting of the Council at which the proposal to elect him as an Honorary Fellow is voted upon, and shall also be available in the Society's Rooms for inspection by Fellows for not less than ten days immediately prior to such meeting.

14. Honorary Fellows shall not be required to contribute to the Funds of the Society, and shall not vote at any General Meeting of the Society or be eligible for office, but in other respects they shall enjoy all the privileges of Fellowship.

Part III.—*The Resignation and Re-admission of Fellows.*

15. Except in special circumstances determined by the Council, the resignation of any Fellow shall be accepted only after payment of all moneys due from him to the Society. Any person whose resignation from the Fellowship has been duly accepted may present to the Council a request for re-admission. The case of such a person shall then be considered by the Council, which may, if it sees fit, reinstate him as a Fellow.

Part IV.—*The Removal of Fellows.*

16. Unless otherwise determined by the Council, any Fellow who at the date of the Annual General Meeting of the Society shall owe more than one annual subscription, such subscriptions having been applied for and no reason satisfactory to the Council having been assigned for non-payment, shall cease to be a Fellow of the Society. Provided, nevertheless, that on an application for re-admission being addressed to the Council by a person so circumstanced, the case of such person shall be considered by the Council, which may, if it sees fit, reinstate him as a Fellow of the Society on his paying the arrears of his subscriptions, or such portion thereof as the Council may determine, and all other moneys due from him to the Society.

17. The Council shall have the power to expel from the Society any Fellow who has been convicted by a competent tribunal of felony, embezzlement, larceny, or misdemeanour.

18. Any proposal to remove a Fellow from the Society for causes other than those set forth in Bye-Laws 16 or 17 must be made to the Council in writing by at least twenty Fellows, and the Fellow in question shall be given an opportunity of appearing before the Council or of otherwise replying to any charges made against him. If thereafter the proposal for removal is approved by the Council at a meeting thereof he shall cease to be a Fellow of the Society.

Part V.—*The Constitution of the Council.*

19. The Council shall consist of:

(*a*) The President,
(*b*) The Vice-Presidents,
(*c*) The Honorary Treasurer,
(*d*) The Honorary Secretaries,
(*e*) The Chairman of the Publication Committee,
(*f*) The Chairman of the Chemical Council, if a Fellow of the Society,
(*g*) The Chairman of the Joint Library Committee mentioned in Bye-Law 66, if a Fellow of the Society, or if he be not a Fellow of the Society, then one of the Society's representatives serving on and appointed by such Committee as its representative on the Council.

(All of the above shall be *ex-officio* members of the Council.)

(*h*) Ordinary Members to be elected from amongst the Fellows in the manner hereinafter provided, who shall be, and are herein termed, " elected Ordinary Members," and
(*i*) such (if any) additional Ordinary Members, not exceeding two in number, as may be appointed by the Council under Bye-Law 20 who shall be, and are herein termed, " co-opted members."

20. The Council shall have power at any time and from time to time to appoint any Fellow as an additional Ordinary Member of the Council to hold office for such period not exceeding three years as the Council may at the time of the appointment determine, but so that at no time shall more than two Fellows be members of the Council pursuant to any such appointment.

21. The President, the Honorary Treasurer, and the Honorary Secretaries for the time being shall be the Officers of the Society and are herein termed " the Officers."

22. The Council shall manage and superintend the affairs of the Society, and may exercise all the powers conferred upon it by the Society's Charters and these Bye-Laws and generally all such powers of the Society as are not by the Charters or these Bye-Laws required to be exercised by the Fellows in General Meetings.

Part VI.—*The Election of the Council.*

23. An election to fill vacancies on the Council shall be held annually in the manner hereinafter provided, and the result of the election shall be declared at the Annual General Meeting.

24. In the month of December a list shall be prepared by the Council of the vacant places in the Council which fall due to be filled at the Annual General Meeting. Such list shall as regards each vacancy amongst the elected Ordinary Members of the Council specify the constituency in which it occurs. The list shall be read at a Scientific Meeting, and shall be published in the Society's *Proceedings*. The Council shall at the same time and in the same manner intimate the names of any persons whom it proposes to nominate for the offices of President, Honorary Treasurer, and Honorary Secretaries, should there be a vacancy in any of these offices.

25. A nomination for any vacancy among the Officers or among the Vice-Presidents who have not filled the office of President may be made in writing signed by at least twenty Fellows, and must be received by the Honorary Secretaries at the Society's Rooms not later than the Fourteenth day of February. Every such nomination must relate to one vacant place only, and must be accompanied by a signed declaration by the nominee that he is willing to accept office if elected. The Council may, not later than its meeting in February, nominate any Fellow of the Society to fill any vacancy amongst the Vice-Presidents who have not filled the office of President.

26. Representation of the general body of Fellows on the Council shall be on a territorial basis having regard to the number of Fellows resident in the several areas (herein termed " constituencies ") defined in the territorial representation scheme set forth in the appendix

hereto, and the nomination of candidates to fill vacancies (other than casual vacancies) occurring amongst the elected Ordinary Members of the Council and the election of persons to fill such vacancies shall be governed by the provisions relating thereto hereinafter contained.

27. The Council shall have power at any time and from time to time to alter the territorial representation scheme in any manner it may think fit, but no such alteration shall be effective unless and until it be approved by the Fellows in General Meeting. References herein to the "territorial representation scheme" shall be deemed to be references to the scheme for the time being in force.

28. A Fellow having residences or business or professional addresses in two or more constituencies shall be entitled to choose, but if he shall not do so the Council shall decide, in which one of such constituencies he is to be treated as resident for the purposes of the territorial representation scheme.

29. A constituency under the territorial representation scheme shall not be entitled to be represented on the Council unless the number of Fellows resident therein shall exceed seventy, and accordingly on the annual election to fill vacancies in the Council nominations of candidates for election as elected Ordinary Members shall be receivable only from those constituencies the number of Fellows resident in which on the previous Thirty-first day of December exceeded seventy. Provided that no elected Ordinary Member of the Council shall vacate office by reason only of the fact that the number of Fellows resident in the constituency he represents falls below the limit aforesaid during his period of office as an elected Ordinary Member of the Council.

30. If on the occasion of any election of elected Ordinary Members of the Council there shall be any constituency which under the last preceding Bye-Law shall not be entitled to representation on the Council, the place or places on the Council allotted to that constituency under the territorial representation scheme shall not be filled, but shall remain vacant until such time as there shall be an annual election on the occasion of which nominations for filling such place or places on the Council shall be receivable from that constituency pursuant to the last preceding Bye-Law.

31. Upon the occasion of any annual election to fill vacancies in the Council Fellows resident in a constituency may nominate any Fellow of the Society resident in that constituency for election to the Council to fill a vacancy amongst the number of elected Ordinary Members of the Council allotted to that constituency under the territorial representation scheme and requiring to be filled at such election. Every such nomination must be in writing signed by at least fifteen Fellows resident in the constituency. It must relate to one vacant place only and be received by the Honorary Secretaries at the Society's Rooms not later than the Fourteenth day of February accompanied by a signed declaration by the nominee that he is willing to accept office if elected.

32. If the number of nominations received as aforesaid by the Fourteenth day of February in respect of any constituency shall be less than the number of vacancies amongst the elected Ordinary Members for that constituency then requiring to be filled, the Council shall have power to nominate a sufficient number of Fellows to fill all or any of the remainder of such vacancies for that constituency. Except as by this Bye-Law provided and saving the power of the Council to fill casual vacancies, the Council shall have no power to nominate candidates to fill vacancies amongst the elected Ordinary Members of the Council.

33. Forthwith after the Fourteenth day of February in each year the Council shall prepare a list of all candidates who have been duly nominated as aforesaid for filling the vacancies amongst the Officers, the Vice-Presidents, and the elected Ordinary Members of the Council respectively, and shall state therein as regards the last mentioned the constituency for which each candidate has been nominated. A copy of such list shall be sent, in the manner provided in Bye-Law 73, to each Fellow entitled to receive notices, and shall be read at a Scientific Meeting.

34. If by reason of the death after the preparation of the said list of any Fellow named therein there shall not remain another Fellow nominated to fill a vacancy amongst the Officers or the Vice-Presidents or a sufficient number of Fellows nominated to fill all the vacancies for any constituency, there shall be deemed to have arisen a casual vacancy which shall be filled by the Council pursuant to Bye-Law 42 with effect from the Annual General Meeting.

35. If in the case of Officers, or of Vice-Presidents, or of elected Ordinary Members for any constituency the number of nominations duly made for filling the vacancies amongst them respectively shall not exceed the number of such vacancies, the persons nominated shall be declared duly elected at the Annual General Meeting without any vote being taken.

36. If as regards the Officers, or the Vice-Presidents, or the elected Ordinary Members for any constituency, more candidates are nominated than there are vacant places, the Honorary Secretaries shall, not less than fourteen days before the Annual General Meeting, send, in the manner provided in Bye-Law 73, to each Fellow entitled to receive notices, a ballot paper containing a list of the vacancies for which there is a contest and of the names of the candidates nominated therefor, distinguishing as regards the Officers and Vice-Presidents those who have been nominated by the Council, and stating in the case of each candidate for a place as an elected Ordinary Member of the Council the constituency for which he has been nominated. Each ballot paper shall also state the date by which it must be received by the Honorary Secretaries at the Society's Rooms, duly completed, in order to be counted.

37. Upon a ballot for the election of persons to fill vacancies in the Counci each Fellow shall be entitled to one vote for each vacant place to be balloted for amongst the Officers, the Vice-Presidents, and the elected Ordinary Members for each constituency. The Scrutators hereinafter mentioned shall reject any ballot paper completed otherwise than in accordance with this provision.

38. The accidental omission to send a ballot paper to, or the non-receipt of a ballot paper by, any Fellow shall not invalidate any election.

39. In the event of a ballot being required, two Fellows shall be appointed Scrutators at a Scientific Meeting to assist in the subsequent counting of votes. In the event of either or both of these Scrutators being unable to act, it shall be in the power of the President to appoint substitutes.

40. On some day previous to the Annual General Meeting the votes shall be counted by the Scrutators, with the assistance of one of the Honorary Secretaries, and the Scrutators together with the Honorary Secretary shall prepare and sign a report to the Council. A statement of the votes cast for each Candidate shall be presented at the Annual General Meeting, and the Chairman shall declare the names of those duly elected.

41. In any case of equality of votes for two or more candidates in respect of one vacancy, the Council shall decide which of the candidates shall be deemed elected.

42. Any casual vacancy occurring in the Council (other than amongst the *ex-officio* members of the Council mentioned under (*e*), (*f*), and (*g*) in Bye-Law 19) may be filled by the Council from amongst the Fellows, but any such vacancy amongst the elected Ordinary Members of the Council shall be filled only by a Fellow resident in the constituency in respect of which the vacancy occurred. The person chosen by the Council to fill a casual vacancy shall retire from the Council at the next Annual General Meeting, but shall be eligible for re-election to the Council at the election to be held before that meeting.

Part VII.—*The President.*

43. The President shall hold office from the Annual General Meeting at which his election is announced until the second following Annual General Meeting, or, if he has been appointed pursuant to Bye-Law 42, from the date of his appointment until the next following Annual General Meeting.

44. The President shall preside at the meetings of the Society and of the Council and shall regulate the order of the proceedings. In the absence of the President the chair shall be taken by one of the Vice-Presidents or by another member of the Council, and if no member of the Council is present at a meeting of the Society and willing to act, the meeting shall elect a Chairman.

Part VIII.—*The Vice-Presidents.*

45. Of the Vice-Presidents six (or less if six are not available and willing to act) shall be Vice-Presidents who have filled the office of President, and six shall be Vice-Presidents who have not filled the office of President.

46. The President shall upon the expiration of his term of office as President become and be a Vice-President. Any past President becoming or being re-appointed a Vice-President under this Bye-Law shall, if willing, continue to hold the office of Vice-President until there shall be holding office six Vice-Presidents who since himself have filled the office of President, when he shall *ipso facto* vacate the office of Vice-President, but may be re-appointed by the Council if, for any reason, the number of past Presidents willing to continue in office as Vice-Presidents shall fall below six.

47. The six Vice-Presidents who have not filled the office of President shall be elected as provided in Part VI of these Bye-Laws. Their term of office shall be three years, and they shall not be eligible for re-election until after the lapse of one year. Provided that if any of such six Vice-Presidents is nominated for the Presidency before the expiry of his term of office, such nomination, if accepted, shall be deemed to create an additional vacancy in the list of Vice-Presidents.

Part IX.—*The Honorary Treasurer.*

48. The Honorary Treasurer shall hold office until a successor has been appointed.

49. The Honorary Treasurer shall pay all moneys of the Society received by him into the hands of the Society's Banker, retaining only such sums as may be necessary for the payment of current expenses, and shall disburse such sums as may be ordered by the Council. He shall keep accounts of all receipts and payments, and he shall produce such accounts at any meeting of the Council, when required.

50. The Honorary Treasurer shall, on or before the first day of January of each year, send to every Fellow of the Society a notice requesting payment for publications to be supplied in the ensuing year and informing him that his subscription, unless the same shall have been wholly remitted under Bye-Law 9, and except in the case of Life Subscribers, is due.

51. At the Annual General Meeting in each year an Auditor or Auditors, who shall be a Chartered Accountant or Chartered Accountants, shall be appointed to audit the Accounts of the Society for the current year. The remuneration of the Auditors shall be fixed by the Council. A Member of the Council shall not be eligible as an Auditor.

Part X.—*The Secretaries.*

52. There shall be such number of Honorary Secretaries (but not less than two) as the Council shall from time to time determine having regard to the extent and nature of the duties the Honorary Secretaries are called upon to perform, of whom one may be designated as " Honorary Foreign Secretary " by the Council. The Honorary Secretaries, or one of them, shall attend all meetings of the Society and of the Council, and shall be responsible for the accuracy of the minutes prepared by the General Secretary.

53. Each Honorary Secretary shall vacate the office of Honorary Secretary after he shall have held office for six years, and shall not be eligible for re-election as Honorary Secretary until after the lapse of one year.

54. The General Secretary shall be appointed by the Council, by whom his remuneration and terms of service shall be fixed. He shall not be a Fellow of the Society. He shall act under the general direction of the Officers, and subject thereto shall be charged with the general administrative business of the Society, the arrangement of the office work, and the conduct of routine correspondence. It shall be his duty to attend, except as may be determined by the President, all meetings of the Council and to take the minutes thereof.

Part XI.—*The Elected Ordinary Members of the Council.*

55. Subject to Bye-Law 56, the term of office of elected Ordinary Members of the Council shall be three years. A retiring elected Ordinary Member of the Council, other than one whose election to that office was to fill a casual vacancy, shall not be eligible for re-election for the same constituency until after the lapse of one year.

56. An elected Ordinary Member of the Council shall *ipso facto* vacate that office if he shall cease to reside in the constituency for which he was elected or if he shall be appointed to any other position on the Council. Any vacancy thus caused shall be a casual vacancy amongst the elected Ordinary Members of the Council.

Part XII.—*Council Meetings.*

57. The Council shall hold at least eight ordinary meetings in the year at such times as it may determine. Six members shall form a quorum.

58. Notice of the time of holding each meeting of the Council shall be forwarded by one of the Honorary Secretaries to each Member of the Council at least two days previous to that on

which such meeting is to be held, but the accidental omission to give notice of a meeting to, or the non-receipt of notice of a meeting by, any Member of the Council shall in no way invalidate the proceedings of the meeting.

59. Extraordinary meetings of the Council shall be called by the President upon a requisition to him signed by three Members of the Council, or at his own discretion, when he shall direct the Honorary Secretaries to issue notices for the occasion.

60. The ordinary mode of decision on questions before the Council shall be by show of hands or, if demanded, by a ballot of those present. In either case a bare majority of votes shall be effective. In the case of an equality of votes either upon a show of hands or upon a ballot the Chairman shall have a second or casting vote. Any Member of the Council who shall be personally concerned in the question under consideration shall, if requested by the Chairman, retire during the discussion and determination of the same.

61. At the Annual General Meetings the Council shall present a Report on the work of the Society during the preceding calendar year.

Part XIII.—*Committees.*

62. The Council may appoint Committees, the members of which shall be Fellows of the Society, and may delegate to such Committees such of its powers as it may think fit. The constitution of each Committee and the appointment of the members thereof and the quorum for the transaction of business shall be determined by the Council. Every Committee shall report to the Council and shall in the exercise of the powers conferred upon or delegated to it conform to such regulations or directions as the Council may by Standing Orders or otherwise from time to time prescribe or impose. The Officers shall be *ex-officio* members of all such Committees. Vacancies occurring on any Committee may be filled by the Council.

63. Without limiting the generality of the powers contained in the last preceding Bye-Law the following may be included among the Committees: Finance and General Purposes Committee, Publication Committee, and Research Fund Committee.

64. The Council may also co-operate with any other body or bodies having objects similar in whole or part to those of the Society in carrying out any scheme or schemes where combined action with any such body or bodies is considered to be desirable, and may appoint a representative or representatives to serve on any Joint Committee which may be constituted of a representative or representatives of the Society and of a representative or representatives of any such other body or bodies in charge of any agreed scheme. Any representative of the Society so appointed to serve on any such Joint Committee shall be a Fellow of the Society.

65. The Council may delegate to any such Joint Committee any of the powers of the Council requiring to be exercised by such Joint Committee for the effective carrying out of any such scheme, including authority to incur expenditure on behalf of the Society in furtherance of any such scheme to such an extent and subject to such conditions as the Council may determine, provided that any such Joint Committee shall obtain the sanction of the Council prior to any changes of policy or developments which may involve the Society in further or new expenditure beyond that already authorised.

66. Until otherwise determined by the Council the following shall be such a Joint Committee as is referred to in Bye-Law 64:

> The Joint Library Committee constituted pursuant to an Agreement, dated July 1st, 1935, made between the Society, the Royal Institute of Chemistry and the Society of Chemical Industry (or any modified or substituted Agreement to which the Council may hereafter agree on behalf of the Society).

Part XIV.—*Local Representatives.*

67. The Council may appoint Fellows as Local Representatives in such areas and under such conditions as it may from time to time determine. The duties of Local Representatives shall be such as the Council may prescribe and include the arrangement of Scientific Meetings for Fellows in their areas. Such meetings may be arranged by the Local Representative solely on behalf of the Society or jointly in conjunction with the representatives of other bodies.

Part XV.—*Standing Orders.*

68. The Council may from time to time make Standing Orders for the regulation of the business of the Council and Committees, provided that such Standing Orders be not repugnant to anything contained in the Charters or Bye-Laws of the Society. Such Standing Orders may be made, amended, or repealed at any meeting of the Council, provided that notice of any proposed new Standing Order, amendment, or repeal has been given at a preceding meeting of the Council. Such notice shall specify the proposed new Standing Order, amendment, or repeal.

Part XVI.—*Scientific Meetings.*

69. At least ten Scientific Meetings of the Society shall be held from October to June inclusive, the specific days and hours of meeting to be determined by the Council. The ordinary course of business shall be as follows, subject, however, to the control of the Chairman for the time being: 1st. The Minutes of the proceedings of the previous Meeting shall be read and submitted for confirmation. 2nd. Announcements of interest to the Fellows shall be made from the Chair. 3rd. New Fellows shall sign the obligation in the Charter-book, and shall be admitted by the Chairman. 4th. Scientific communications shall be read and discussed, lectures delivered, or other scientific matters dealt with.

Part XVII.—*General Meetings.*

70. The Annual General Meeting of the Society shall be held on the Thirtieth day of March, or on some day near thereto, at such hour as the Council may determine.

71. An Extraordinary General Meeting of the Society shall be summoned at any time by the President, on his receiving a written requisition to do so from the Council or from not less than forty Fellows of the Society. The requisition must state the objects of the Meeting. The President also shall have the power of calling an Extraordinary General Meeting.

72. At least fourteen days' notice shall be given to each Fellow resident in any constituency of all General Meetings of the Society specifying the place, the day, and the hour of the meeting, and the general nature of the business proposed to be transacted thereat.

73. A notice may be given to any Fellow either personally or by sending it by post to him at any address in any constituency that he may have furnished for the purpose. A Fellow who has not furnished any such address shall not be entitled to any notices.

74. At any General Meeting of the Society a motion put to the vote of the meeting shall, subject to the provisions of Bye-Law 82, be decided on a show of hands unless a poll is demanded in accordance with Bye-Law 84 or in any other case is, before or on the declaration of the result of the show of hands, directed by the Chairman or demanded by at least thirty of the Fellows present. No poll shall be directed or demanded on the election of a chairman or on a question of adjournment. Unless a poll be so directed or demanded, a declaration by the Chairman that a motion has on a show of hands been carried, or carried by a particular majority, or lost, shall be sufficient evidence of the decision of the meeting. In case of an equality of votes, whether on a show of hands or on a poll, the Chairman of the meeting at which the show of hands takes place or at which the poll is directed or demanded shall be entitled to a second or casting vote.

75. A poll shall be a poll of all the members entitled to receive notice of the meeting at which the motion was put to the vote, and the manner of taking a poll shall be in the discretion of the Chairman. The Chairman may in his discretion (but without prejudice to the generality of the foregoing) determine that a poll shall be taken by means of postal voting papers and in the event of its so determining the following provisions shall apply:

(*a*) The Council shall as soon as reasonably practicable after the date on which the poll is directed or demanded send a voting paper by prepaid post to each Fellow entitled, under Bye-Law 73, to receive notices. The voting paper shall set out the motion on which the poll has been demanded, shall specify the address to which and the time and date on or before which the voting paper must be returned, and shall in all other respects be in such form as the Council shall determine.

(*b*) At the expiration of the period allowed for the return of voting papers the result of the poll shall be ascertained in such manner as the Council shall direct.

(*c*) The Council shall cause such result to be published as soon as reasonably practicable after the ascertainment thereof in such manner as the Council may determine.

Part XVIII.—*The Publication of Scientific Papers.*

76. The Honorary Secretaries shall mark upon each paper sent to them the date on which they received it from the author.

77. The Society shall have the right to retain the manuscripts and illustrative drawings of all papers sent to the Society.

78. The *Journal* of the Society shall be published at intervals to be determined by the Council. It shall consist of such of the papers which have been communicated to the Society and of such other matter as the Council may determine.

79. (i) Every Fellow who, with a view to its publication by the Society, submits a paper, or other communication shall by so doing undertake :

(*a*) that his communication has not been published and that he will not permit its publication before it is accepted or declined by the Society, and

(*b*) that if it is accepted for publication the Society shall thereupon become entitled to the copyright therein and that he will, when called on to do so, assign to the Society the said copyright, including sole right to print and publish in any form, in any language, and in any part of the world the whole or any part of his communication. The Council shall not refuse any reasonable request from an author to reproduce his own work elsewhere in whole or in part.

The attention of every Fellow who submits a paper or other communication for publication shall be drawn to this Bye-Law.

(ii) Every non-Fellow who submits any paper or other communication with a view to its publication shall be required to sign an undertaking in the terms set out above.

Part XIX.—*The Library.*

80. The books in the possession of the Society shall be allowed to circulate under such regulations as the Council, upon the recommendation of the Joint Library Committee referred to in Bye-Law 66, may from time to time deem advisable.

Part XX.—*The Common Seal and Deeds.*

81. The President shall be responsible for the custody of the Common Seal of the Society. Every deed or writing to which the Common Seal is to be affixed shall be passed and sealed in Council and shall be attested by the Chairman of the meeting at which it is so passed and sealed and by another member of the Council.

Part XXI.—*The Alteration of Bye-Laws.*

82. No proposal for an alteration of the Bye-Laws of the Society shall be considered except at the Annual General Meeting or at an Extraordinary General Meeting of the Society called for the purpose, and such proposal shall require for its adoption a majority of not less than two-thirds of those present and voting.

83. A proposal for the alteration of the Bye-Laws may be put forward either by the Council or by the Fellows. In the latter case the proposal must be sent to the Honorary Secretaries in writing, signed by twenty Fellows at least, and shall not be considered until a Report thereon by the Council has been prepared for submission to the Meeting.

84. Any such alteration of the Bye-Laws shall not come into operation for a period of one month after its adoption during which time a poll of all Fellows resident in the constituencies may be demanded by a requisition signed by not less than thirty Fellows. The manner of taking a poll shall be in the discretion of the Council. The Council may, in its discretion, but without prejudice to the generality of the foregoing, determine that a poll shall be taken by means of postal voting papers and in the event of its so determining the provisions set out in Bye-Law 75 shall apply. If less than two-thirds of the votes recorded at such poll are in favour of such alteration the proposal shall be adjudged to be negatived.

APPENDIX

The Territorial Representation Scheme

Number of Constituency	Area of Constituency	Number of elected Ordinary Members of the Council to which the Constituency is entitled
I	SOUTH-EAST ENGLAND, comprising the following counties: Northamptonshire (including the Soke of Peterborough), Huntingdonshire, Cambridgeshire (including the Isle of Ely), Norfolk, Suffolk, Essex, Middlesex, London, Hertfordshire, Bedfordshire, Buckinghamshire, Oxfordshire, Berkshire, Hampshire (including the Isle of Wight), Surrey, Sussex, Kent, and the Channel Islands	9
II	CENTRAL AND SOUTH-WEST ENGLAND AND SOUTH WALES, comprising the following counties: Staffordshire, Shropshire, Herefordshire, Worcestershire, Warwickshire, Gloucestershire, Wiltshire, Dorsetshire, Somerset, Devonshire, Cornwall, Monmouthshire, Cardiganshire, Radnorshire, Pembrokeshire, Carmarthenshire, Brecknockshire, and Glamorganshire	3
III	NORTH-WEST ENGLAND, NORTH WALES, AND THE ISLE OF MAN, comprising the following counties: Cumberland, Westmorland, Lancashire, Cheshire, Flintshire, Denbighshire, Montgomeryshire, Merionethshire, Caernarvonshire, Anglesey, and the Isle of Man	3
IV	NORTH-EAST ENGLAND, comprising the following counties: Northumberland, Durham, Yorkshire, Derbyshire, Nottinghamshire, Lincolnshire, Leicestershire, and Rutland	3
V	SCOTLAND, comprising the whole of Scotland	2
VI	IRELAND, comprising Northern Ireland and the Republic of Ireland	1
	Total of elected Ordinary Members of the Council ...	21

Provided that a constituency shall not be entitled to be represented on the Council in any year unless the number of Fellows resident therein on Thirty-first December in the previous year shall exceed seventy.

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